

Computational microscopy of membrane proteins: methods and tools

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Outline

- Theoretical Biophysics
- Molecular dynamics (MD) simulations
- Applications of MD simulations in membrane biology
 - Protein-lipid interaction: lipid flippase
- Advanced methods
- Future directions

Theoretical Biophysics

- Microscopic & macroscopic relationships

Microscopic World

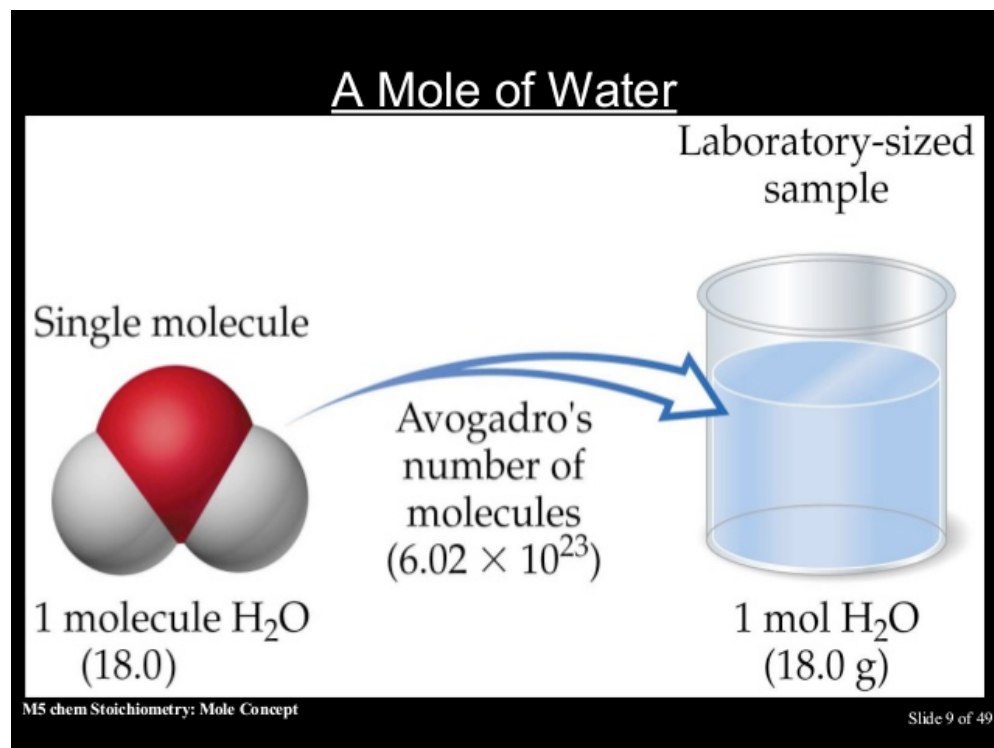
Macroscopic World

Theoretical Biophysics

- Microscopic & macroscopic relationships

Microscopic World

Macroscopic World

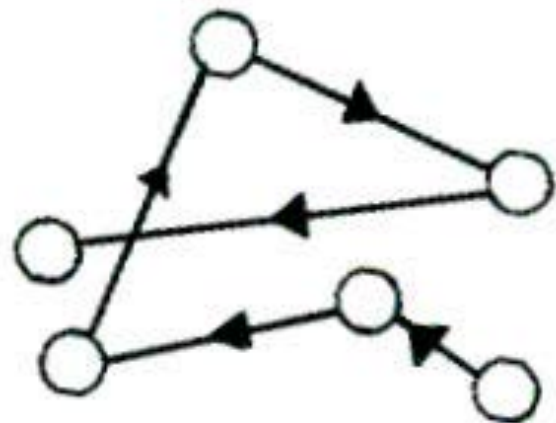


<http://chemistry.tutorvista.com/>

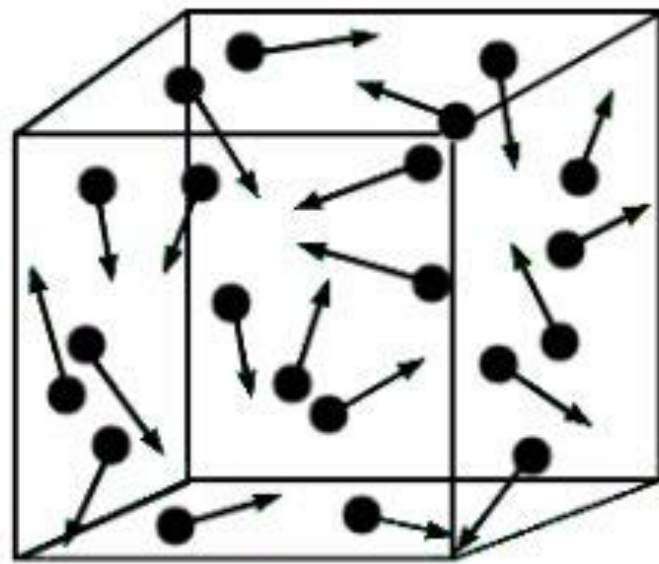
Theoretical Biophysics

- Microscopic & macroscopic relationships

Microscopic World



Macroscopic World

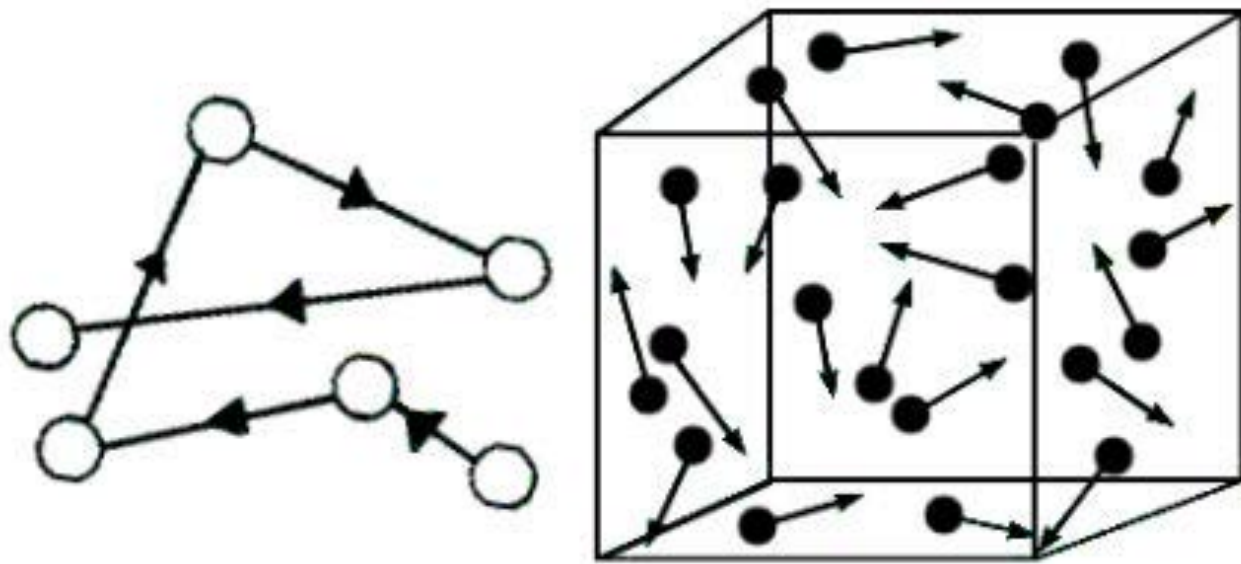


Stochastic Process

Theoretical Biophysics

- Microscopic & macroscopic relationships

Microscopic World



Stochastic Process

Macroscopic World



Pressure

Volume

Theoretical Biophysics

Microscopic World



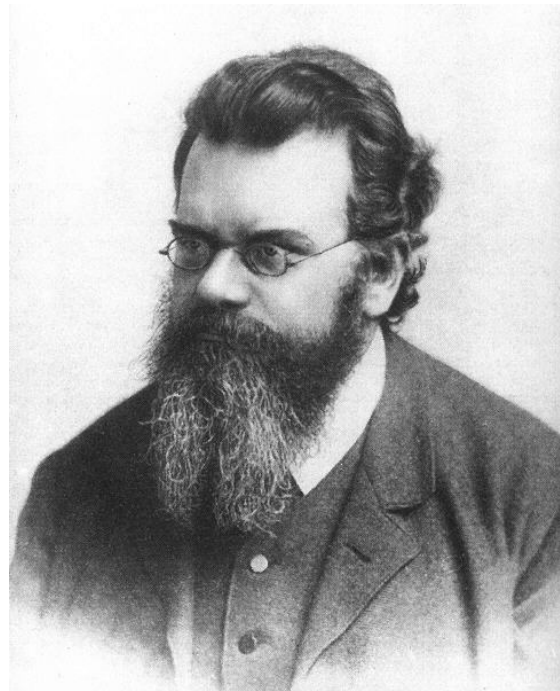
Macroscopic World

Theoretical Biophysics

Microscopic World



Macroscopic World



Ludwig Boltzmann

Founder of statistical mechanic/physics

Theoretical Biophysics

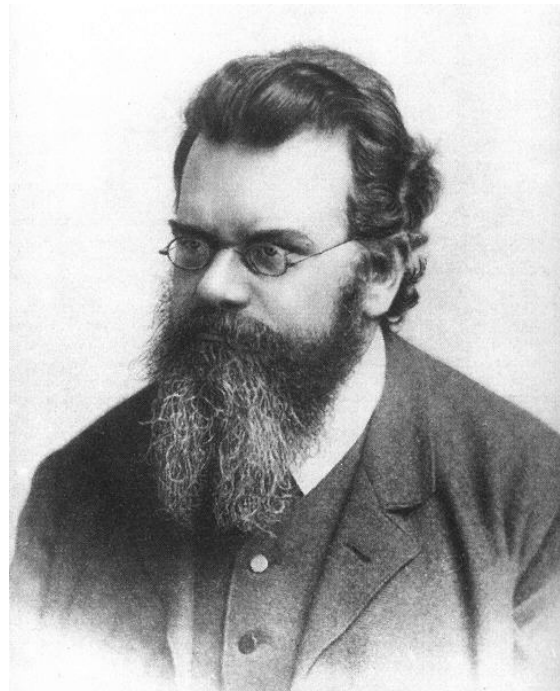
Simple systems

Microscopic World



Macroscopic World

Analytical solutions



Ludwig Boltzmann

Founder of statistical mechanics/physics

Theoretical Biophysics

Microscopic World



Macroscopic World

Theoretical Biophysics

But for complex systems???

Microscopic World  Macroscopic World

Theoretical Biophysics

But for complex systems???



Theoretical Biophysics

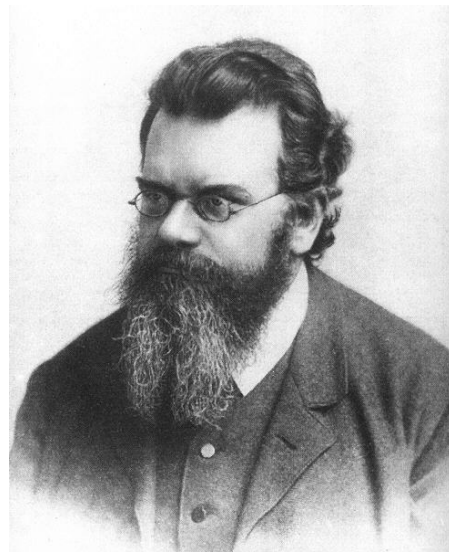
But for complex systems???

Microscopic World



Macroscopic World

Numerical solutions



Ludwig Boltzmann

Founder of Statistical Physics



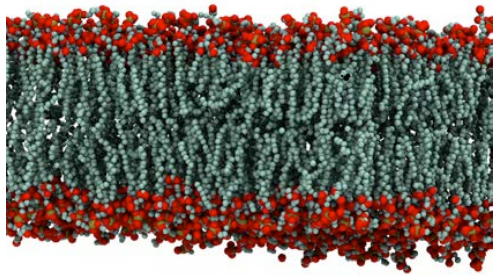
Figure 1. Boltzmann at work (Drawing by Bernhard Reischl, University of Vienna).

Ludwig Boltzmann, in 21st centry

Methods overview

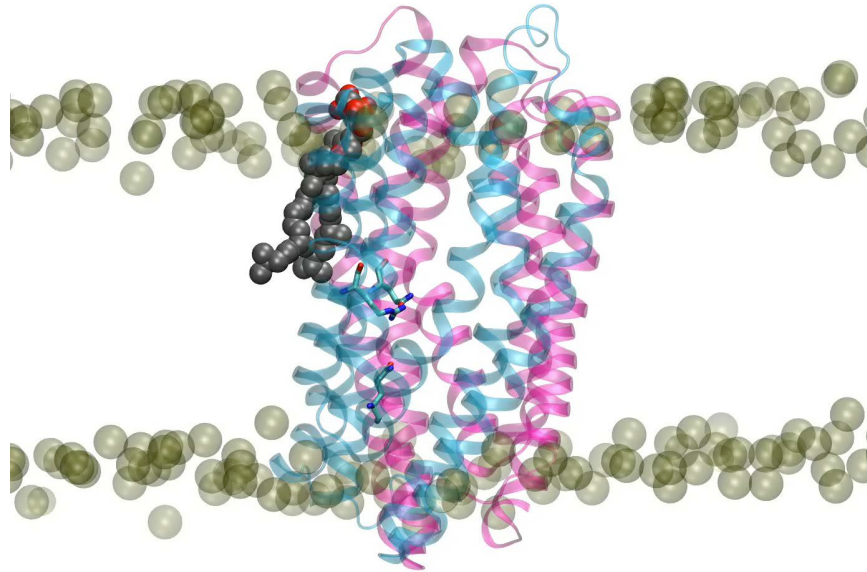
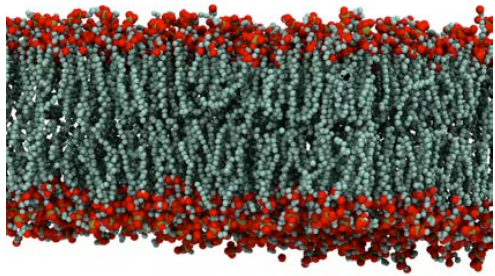
Methods overview

Molecular dynamics simulation



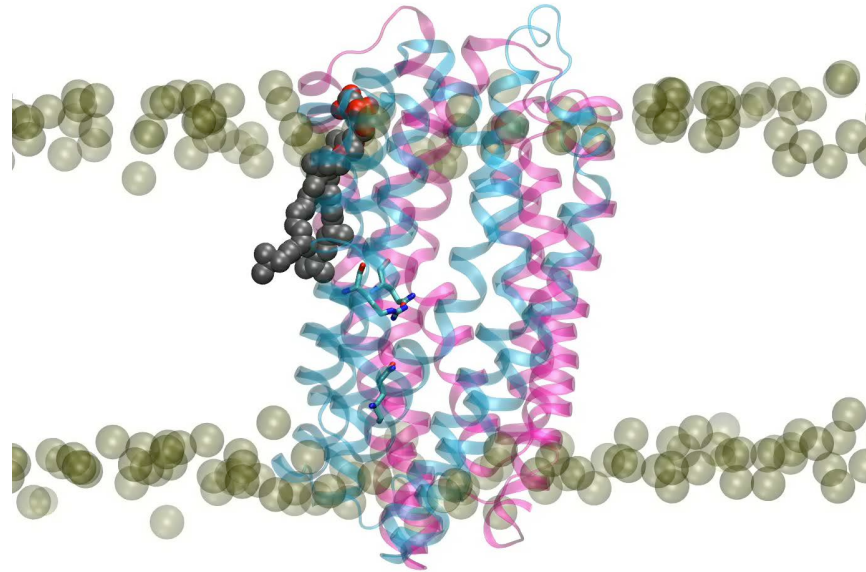
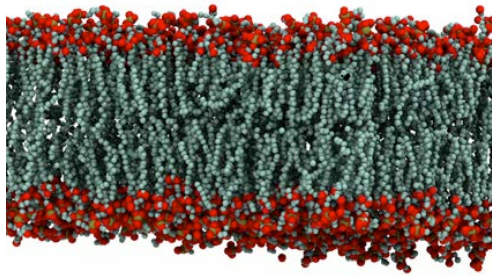
Methods overview

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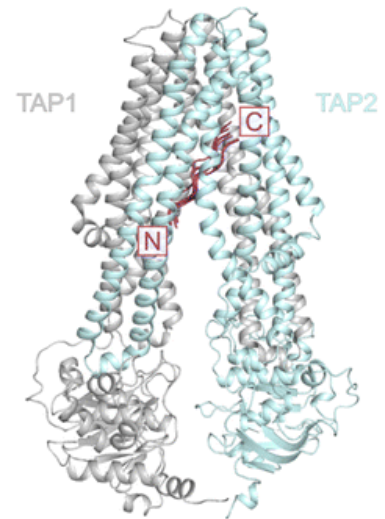
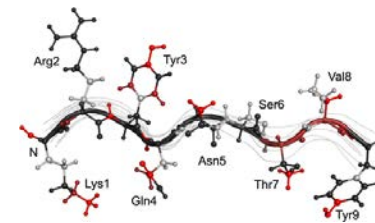


Methods overview

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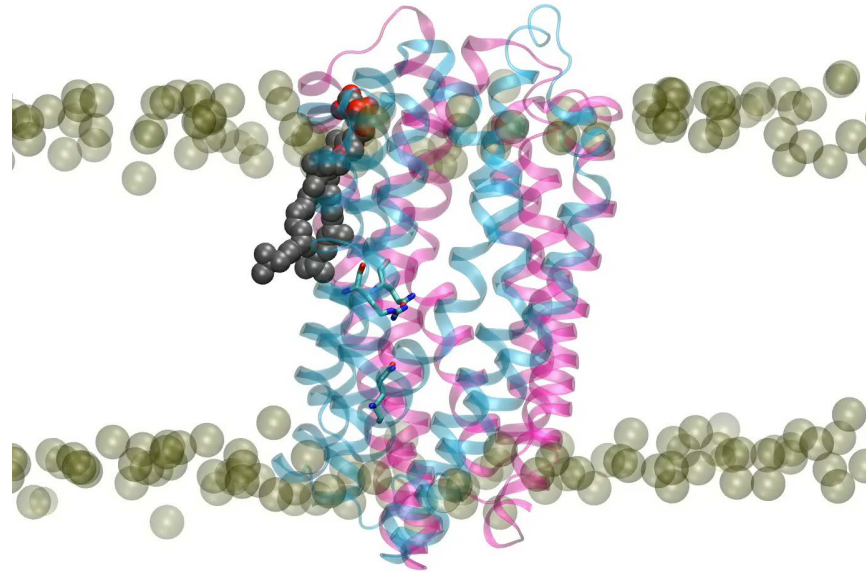
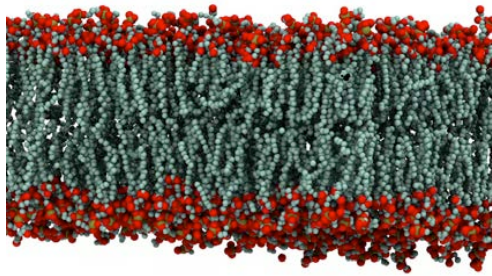


Molecular docking

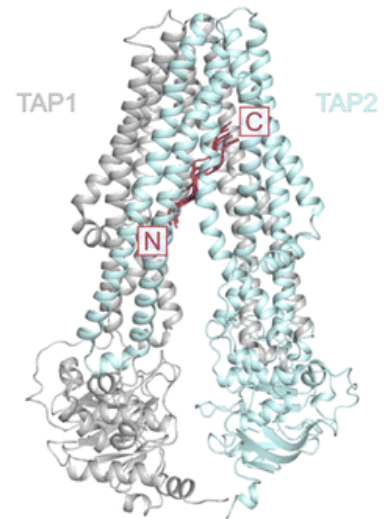
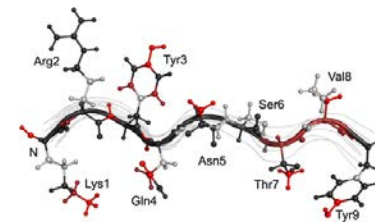


Methods overview

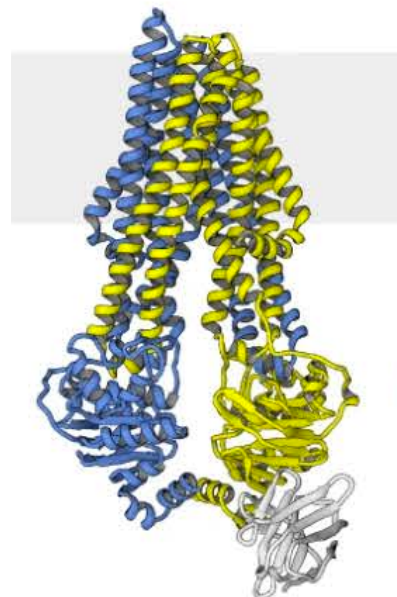
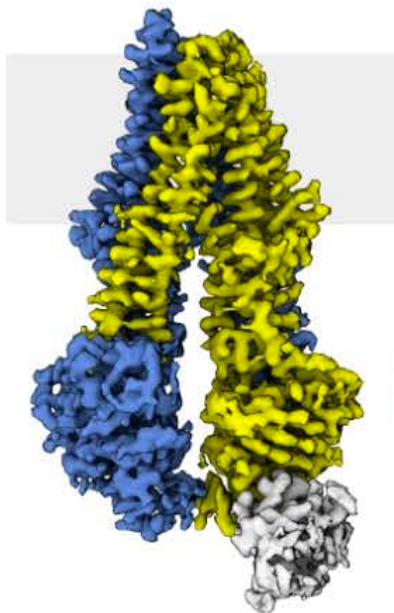
Molecular dynamics simulation



Molecular docking

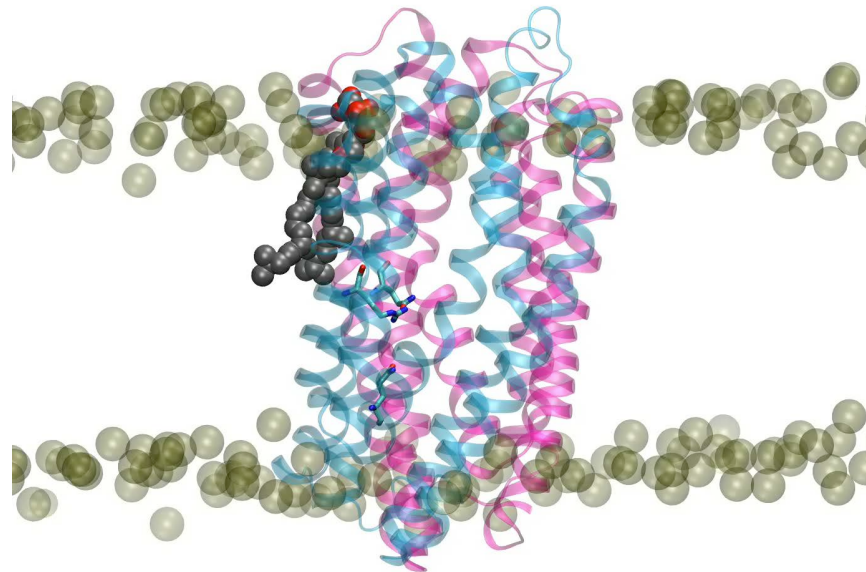
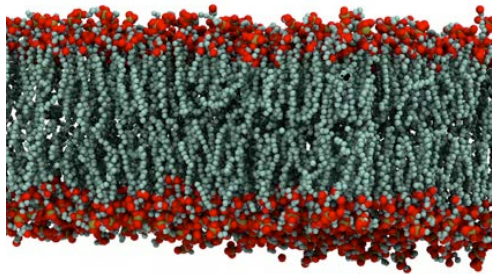


Integrative modeling

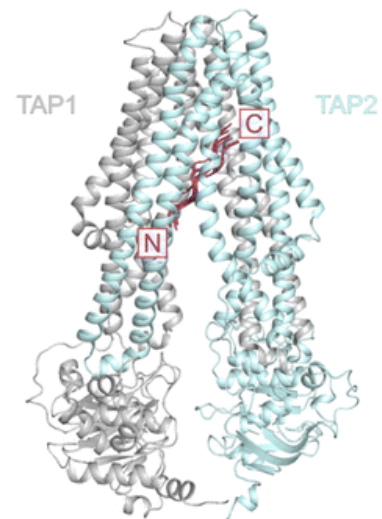
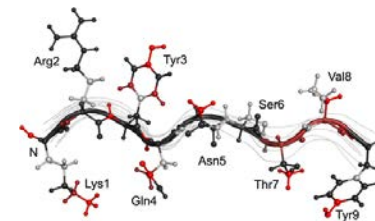


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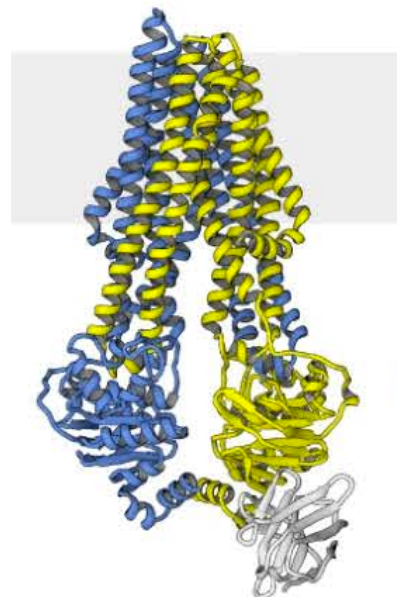
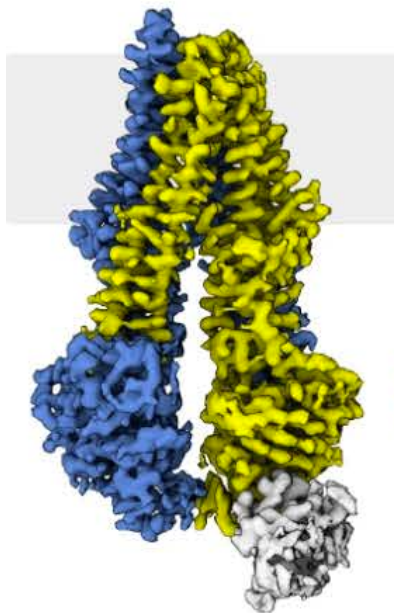
Molecular dynamics simulation



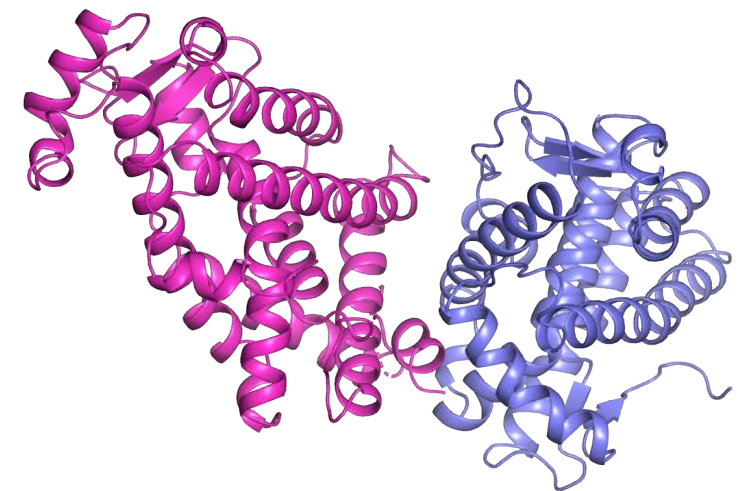
Molecular docking



Integrative modeling

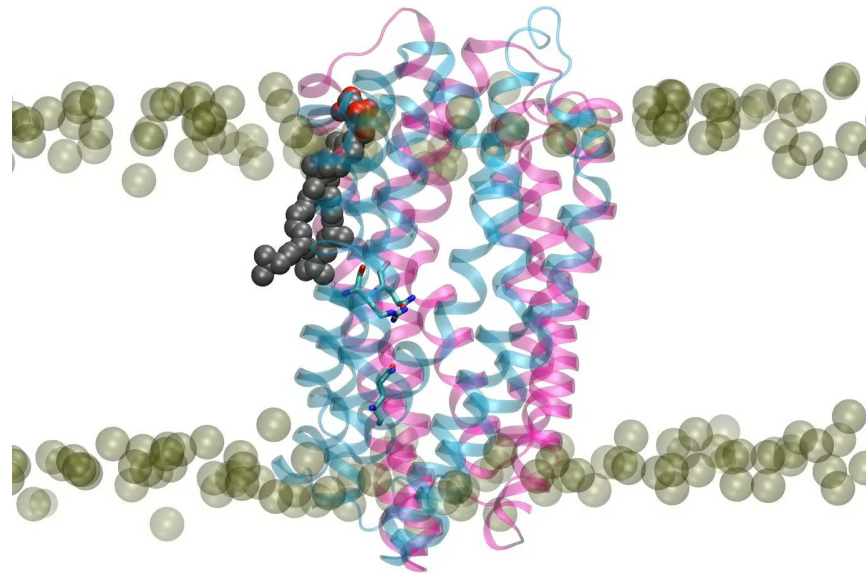
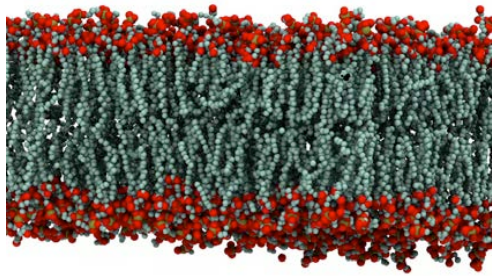


Structural bioinformatics

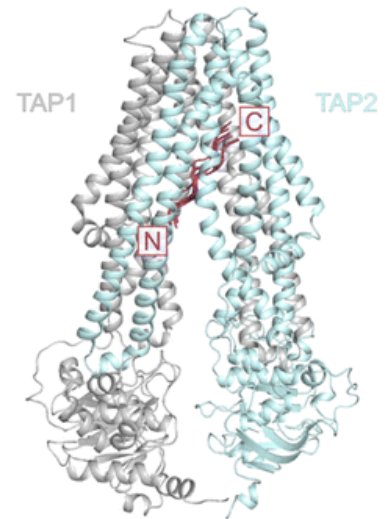
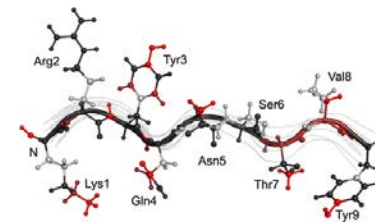


Methods overview

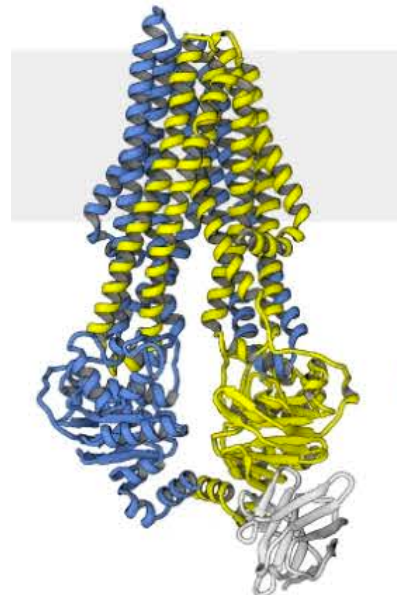
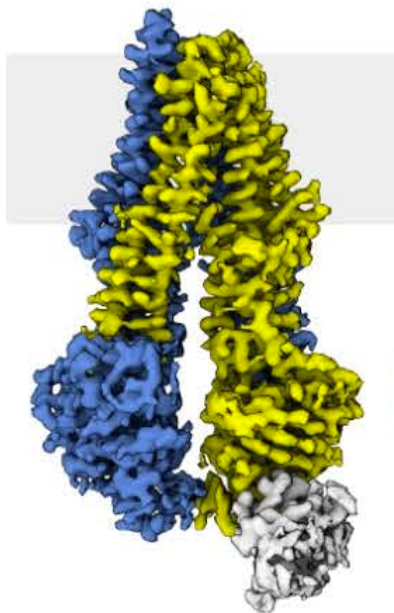
Molecular dynamics simulation



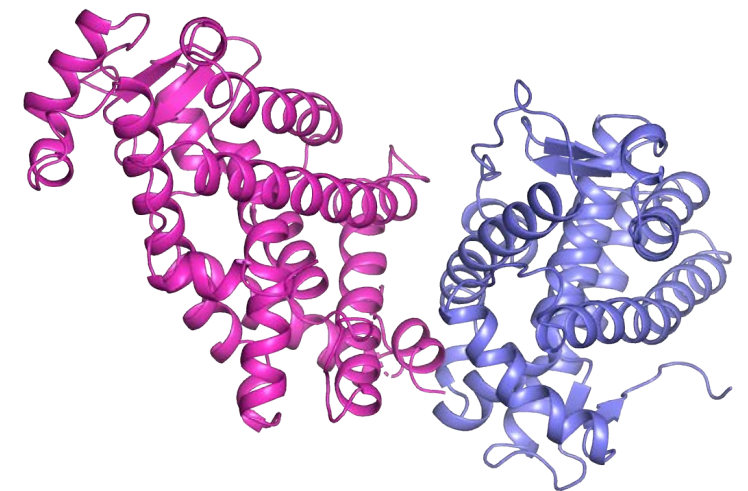
Molecular docking



Integrative modeling

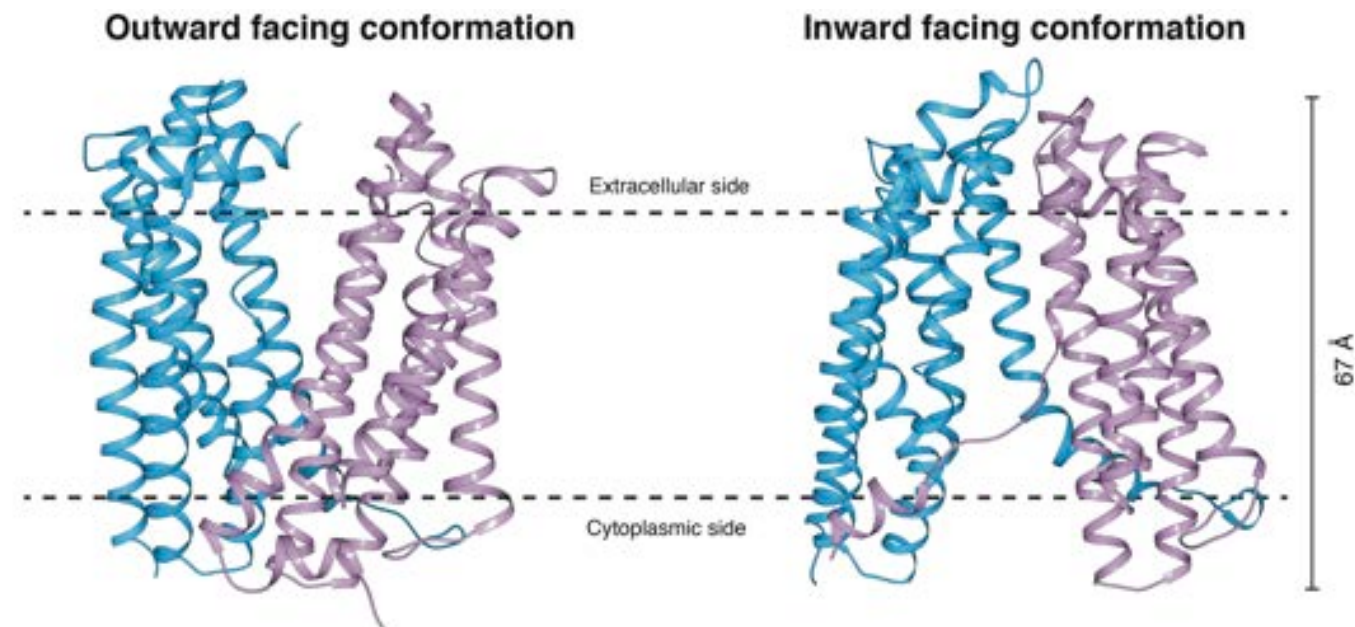


Structural bioinformatics



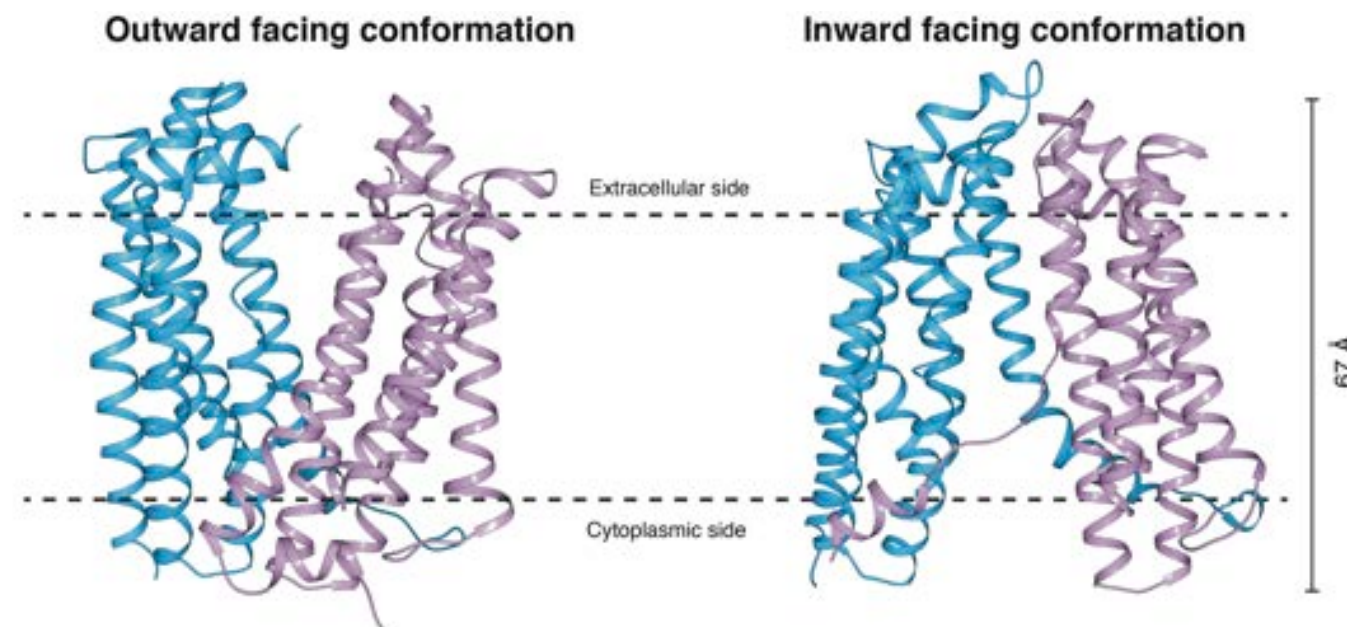
Structures are snapshots

Structural information
Static

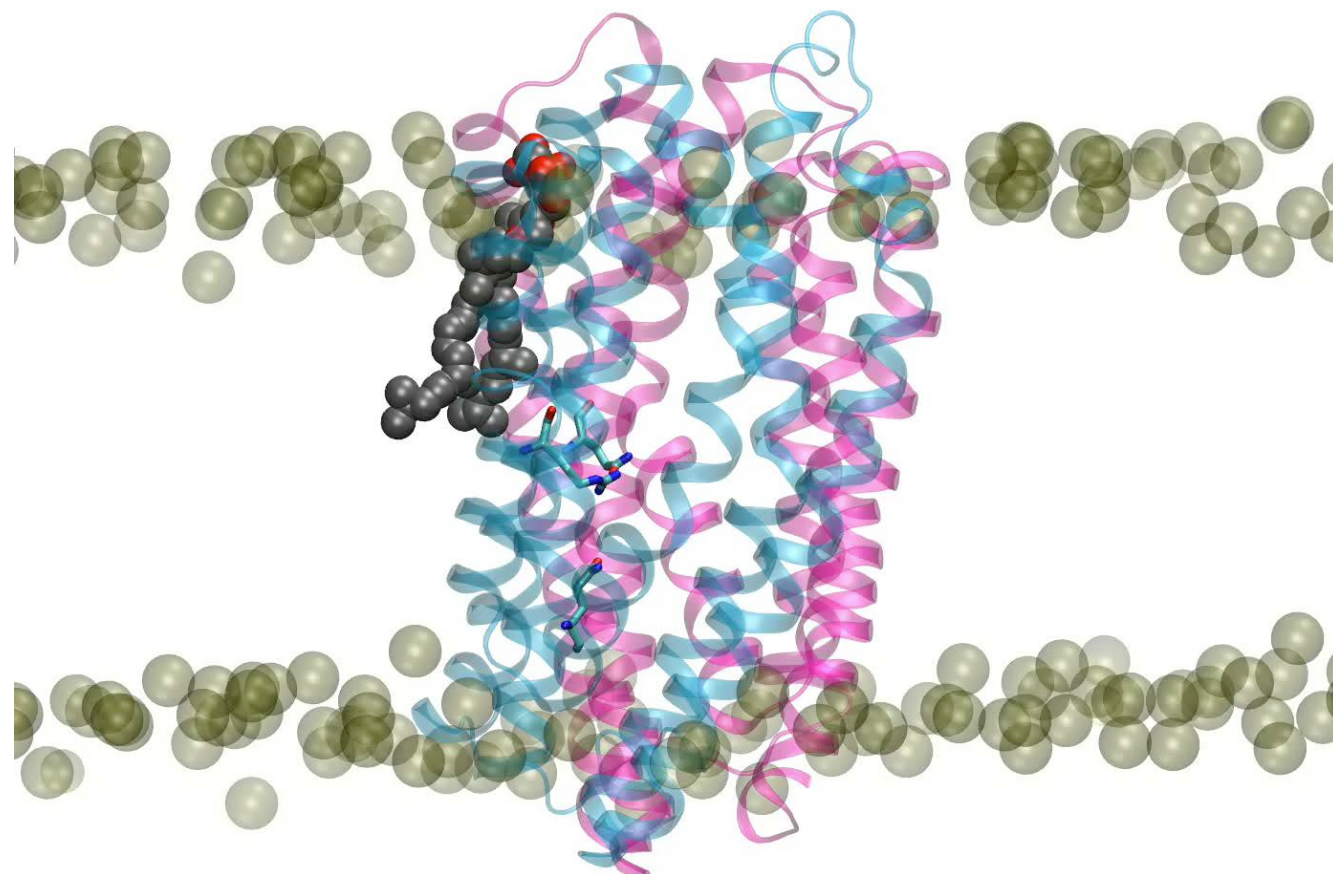


Structures are snapshots

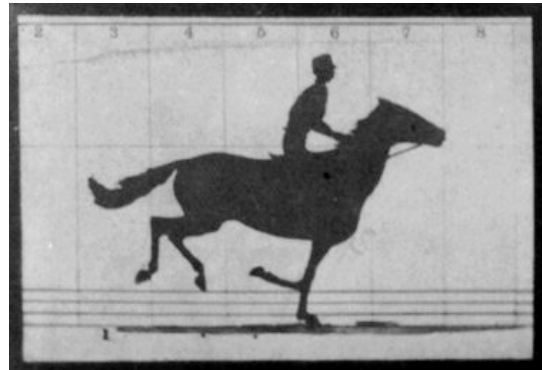
Structural information
Static



Structural information
Dynamic

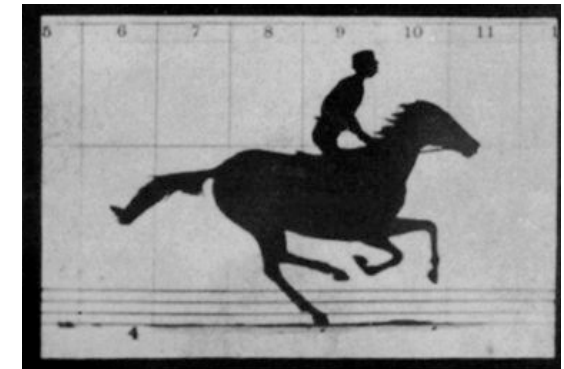
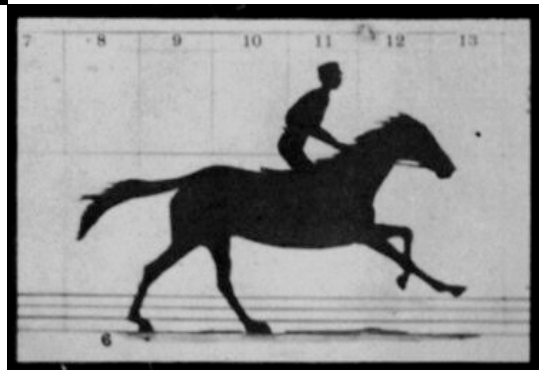
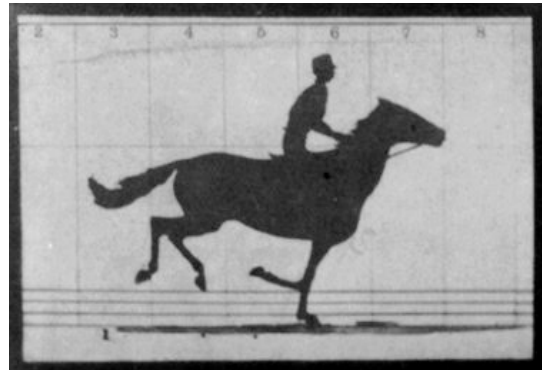


Dynamics as time-resolved phenomenon



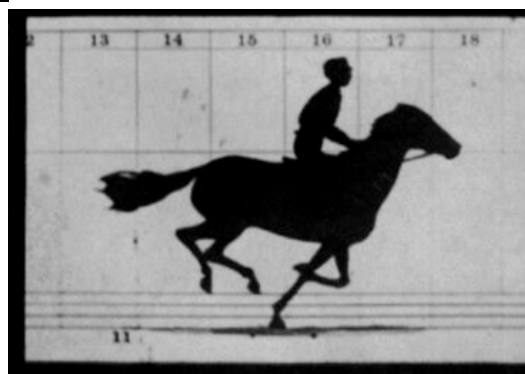
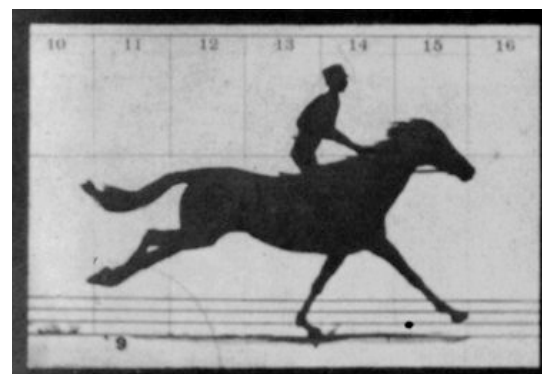
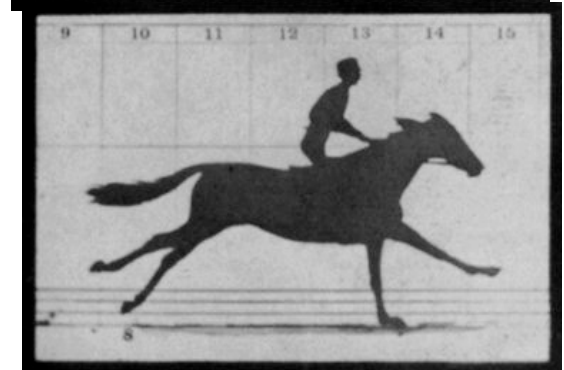
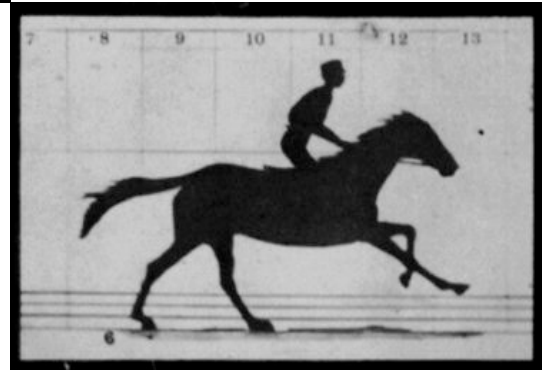
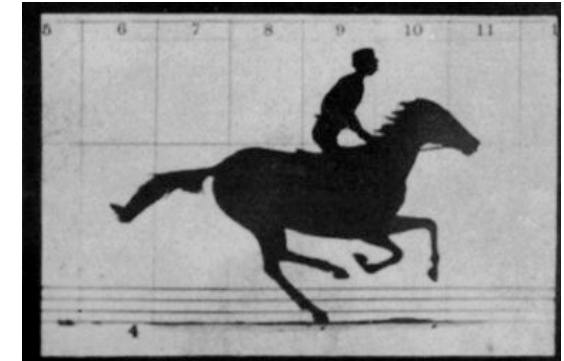
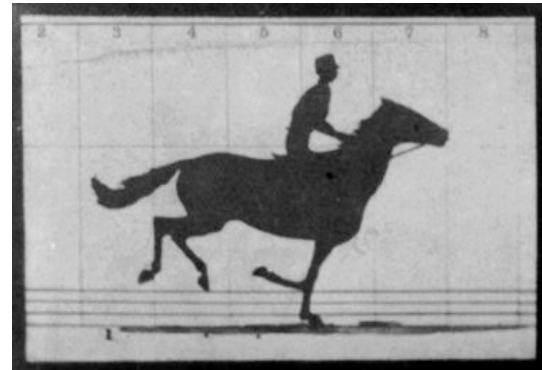
From Eadweard Muybridge - Library of Congress Prints and Photographs Division; <http://hdl.loc.gov/loc.pnp/cph.3a45870>, Gemeinfrei

Dynamics as time-resolved phenomenon



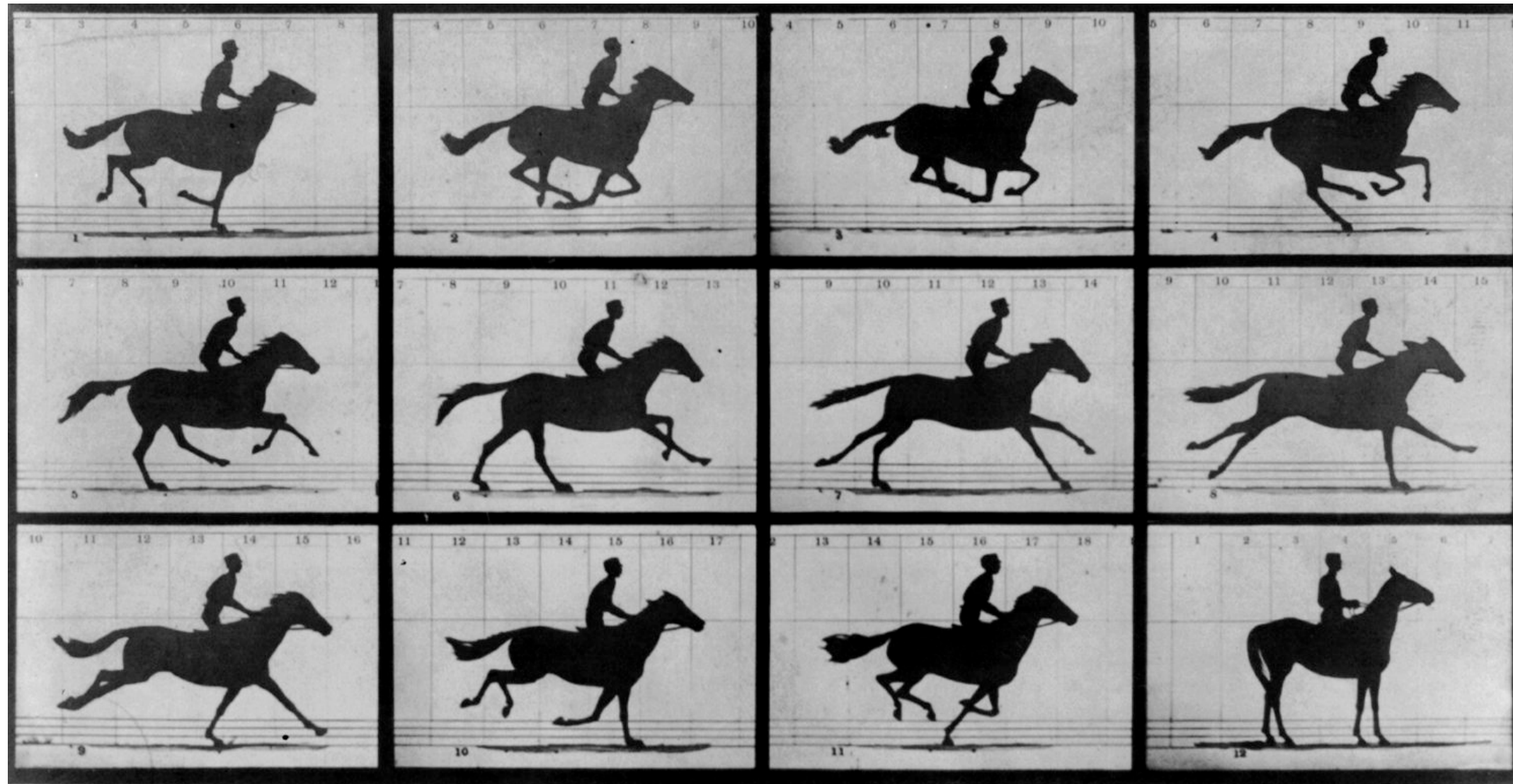
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Dynamics as time-resolved phenomenon



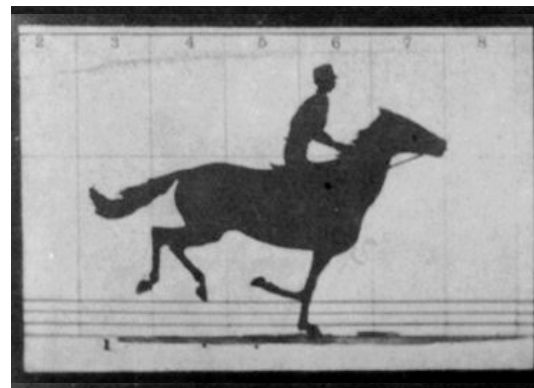
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Dynamics as time-resolved phenomenon



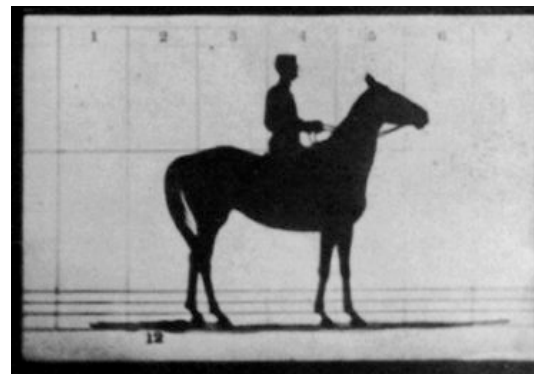
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Dynamics as time-resolved phenomenon



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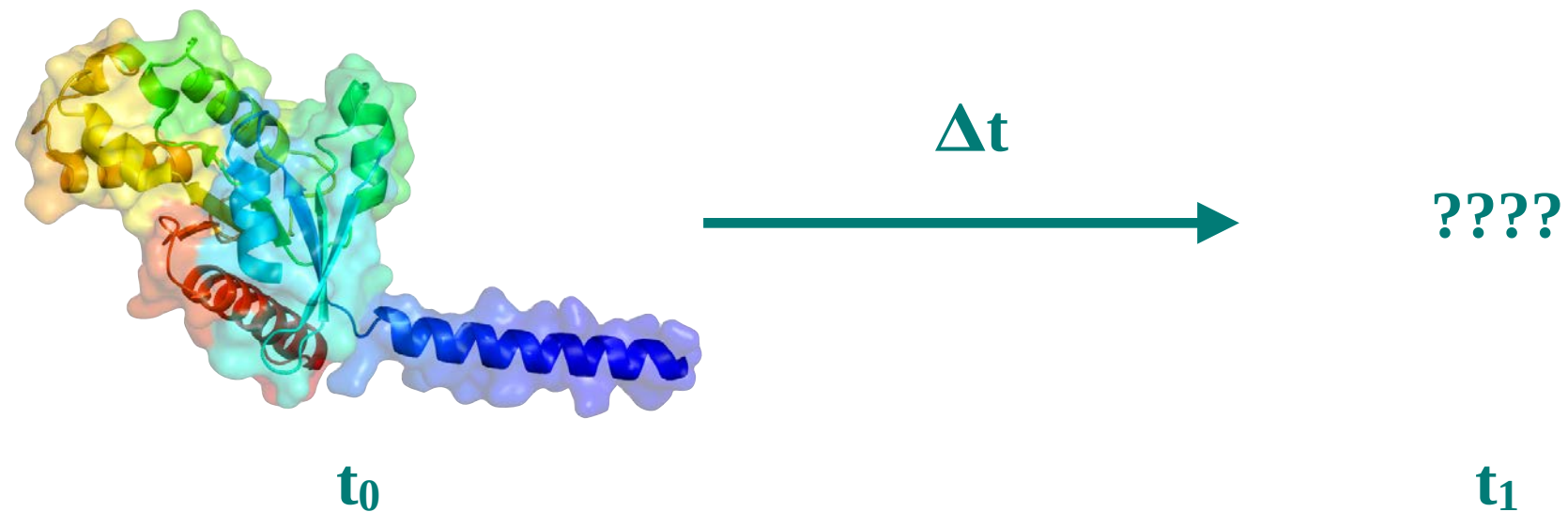
Dynamics as time-resolved phenomenon



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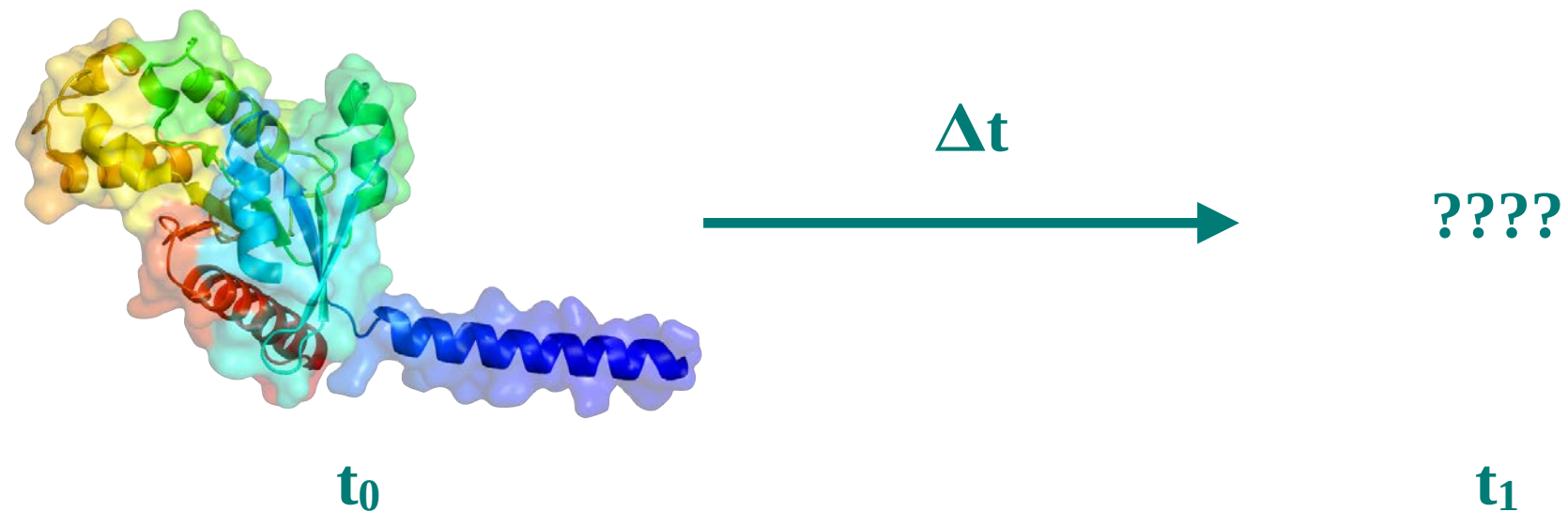
Principles of molecular dynamics simulations

How can we capture the dynamics of biomolecules?



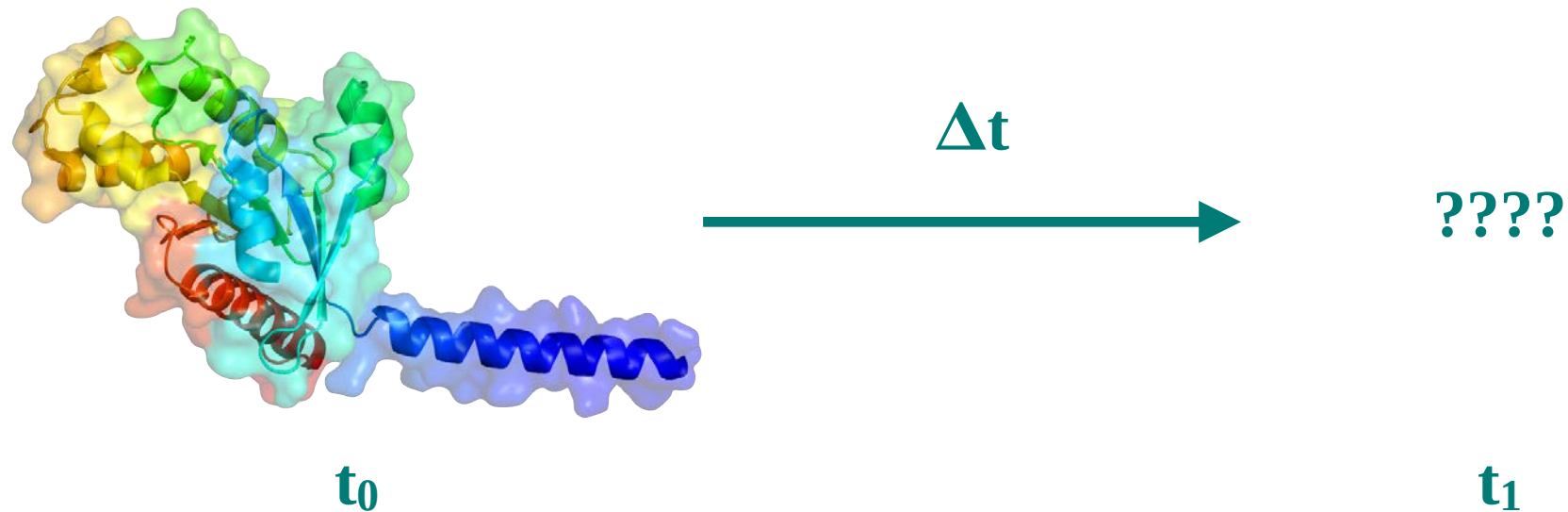
Newton to rescue

How can we capture the dynamics of biomolecules?



Newton to rescue

How can we capture the dynamics of biomolecules?



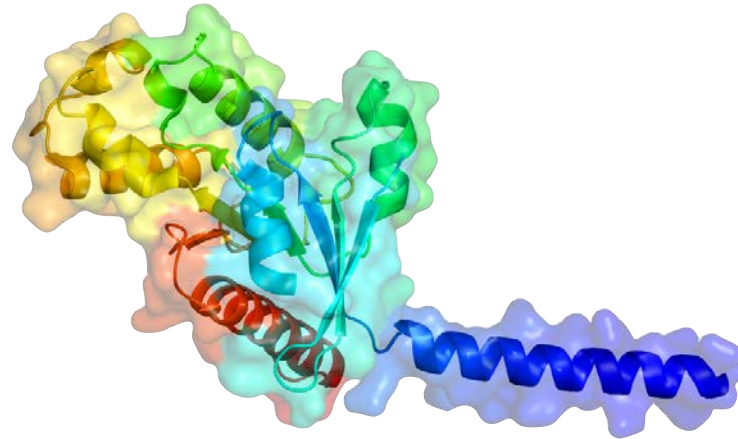
Mass
Coordinates
Velocities
Accelerations



Newton to rescue

Consider a protein at time t

Mass
Coordinates
Velocities
Accelerations



Δt



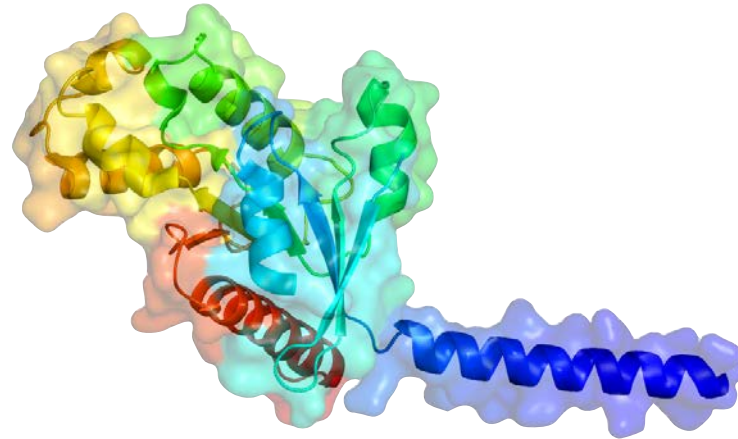
????

Where will all atoms of the protein be at time $t + \Delta t$?

Newton to rescue

Consider a protein at time t

Mass
Coordinates
Velocities
Accelerations



Δt



????

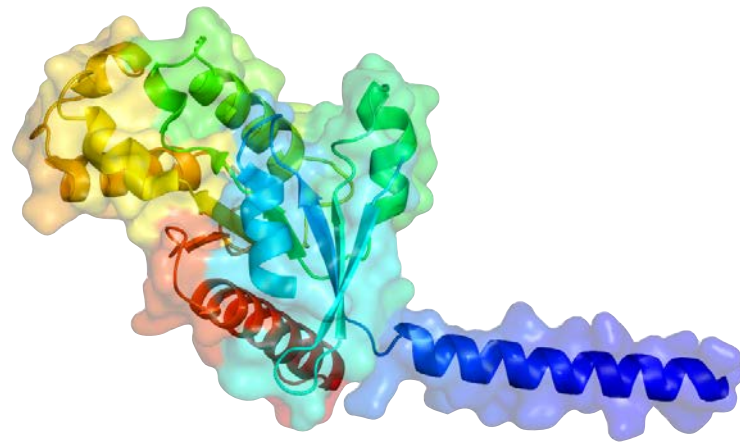
Where will all atoms of the protein be at time $t + \Delta t$?

$$F = ma$$

Newton to rescue

Consider a protein at time t

Mass
Coordinates
Velocities
Accelerations



Δt



????

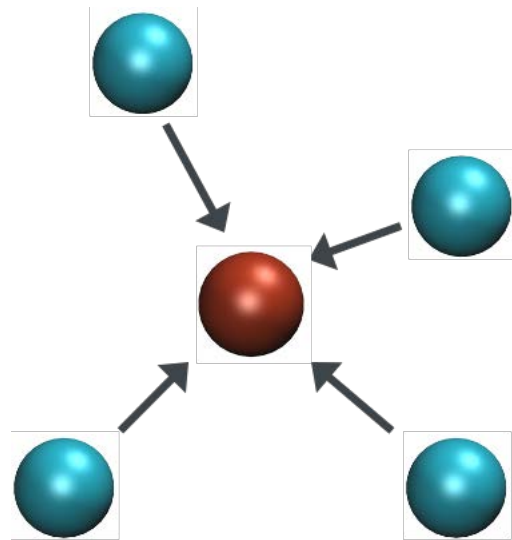
Where will all atoms of the protein be at time $t + \Delta t$?

$$F = ma$$

Solution: **discretised time step (Δt).**

$$r_i(t_0) \longrightarrow r_i(t_0 + \Delta t) \longrightarrow r_i(t_0 + 2\Delta t) \longrightarrow r_i(t_0 + 3\Delta t) \longrightarrow r_i(t_0 + n\Delta t)$$

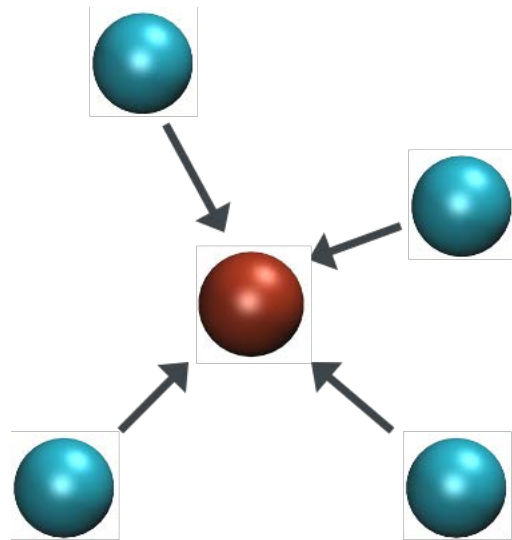
We need to calculate the force!



Potential energy

$$F = \frac{-\partial U(r)}{\partial r}$$

We need to calculate the force!



Potential energy

$$F = \frac{-\partial U(r)}{\partial r}$$

Potential energy or force field

$$U(r) = U_{\text{Bond}} + U_{\text{Angle}} + U_{\text{Dihedral}} + U_{\text{Coulomb}} + U_{\text{VdW}}$$

We need to calculate the force!

$$F = \frac{-\partial U(r)}{\partial r}$$

Our potential function or 'force field' is defined by **bonded** and non-bonded interactions.

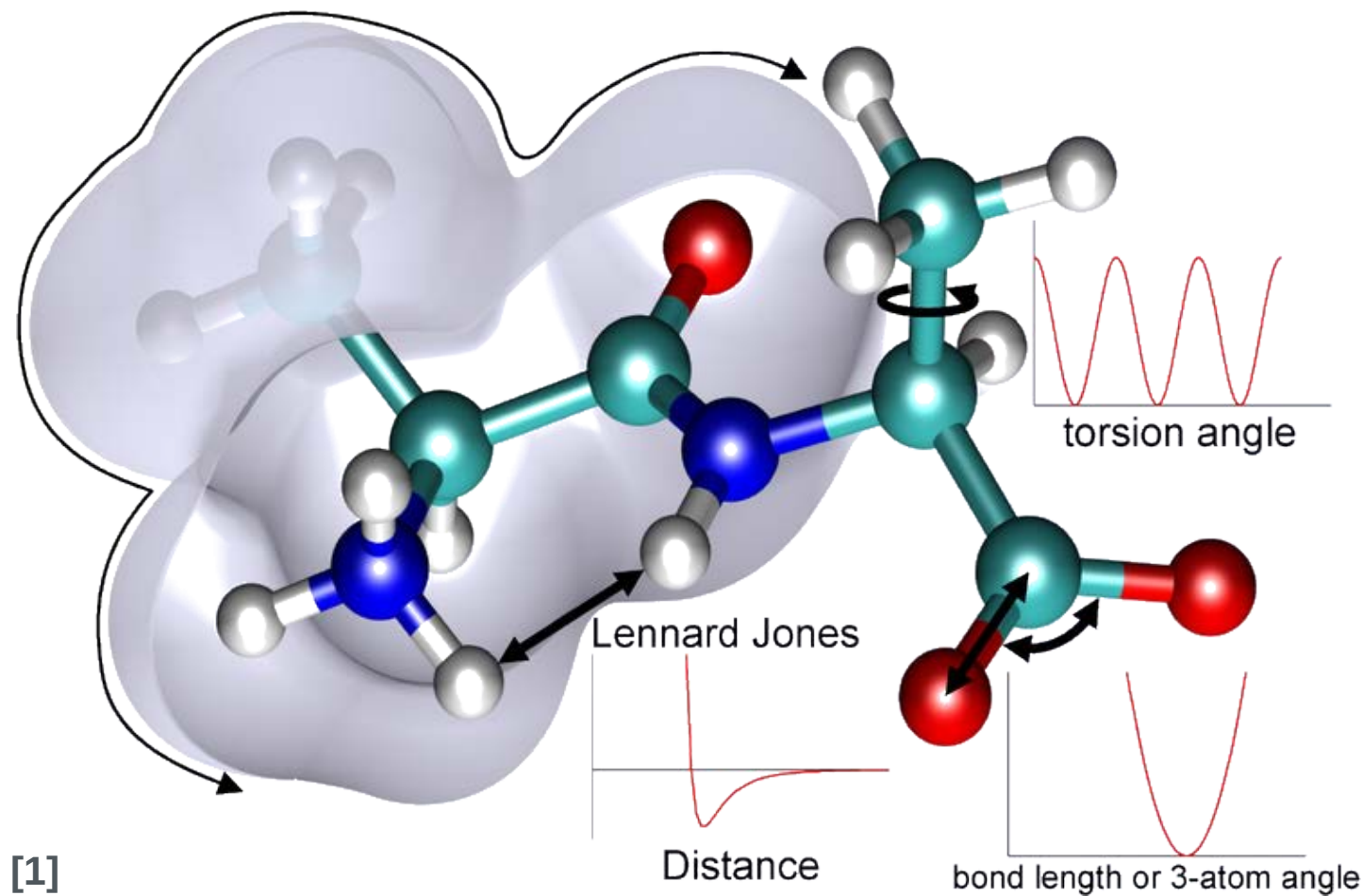
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[1]

[1] force field / Edboas CC BY-SA 3.0

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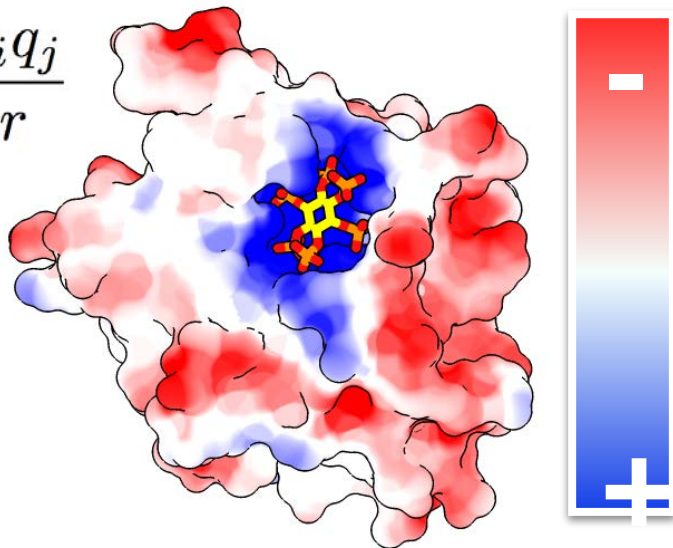
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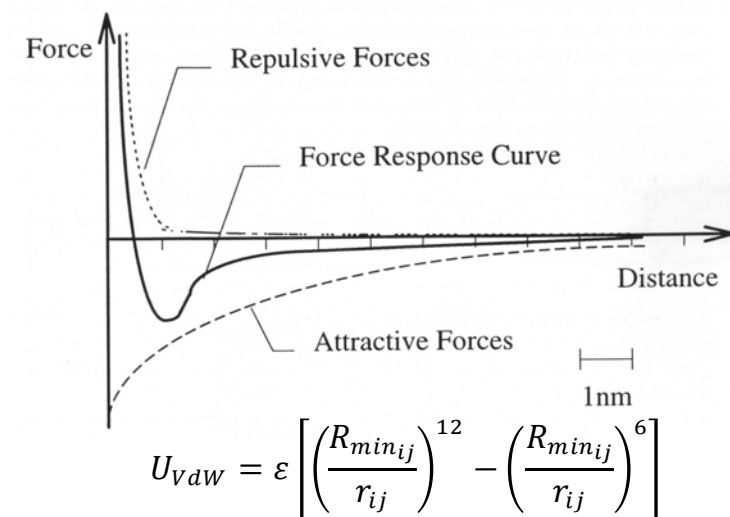
$$U(r) = U_{\text{Bond}} + U_{\text{Angle}} + U_{\text{Dihedral}} + U_{\text{Coulomb}} + U_{\text{VdW}}$$

Electrostatic interaction

$$V_C = \frac{1}{4\pi\epsilon_0\epsilon_r} \frac{q_i q_j}{r}$$



van der Waals forces



We need to calculate the force!

$$F = \frac{-\partial U(r)}{\partial r}$$

Our potential function or '**force field**' is defined by bonded and non-bonded interactions.

$$U(r) = U_{\text{Bond}} + U_{\text{Angle}} + U_{\text{Dihedral}} + U_{\text{Coulomb}} + U_{\text{VdW}}$$

We need to calculate the force!

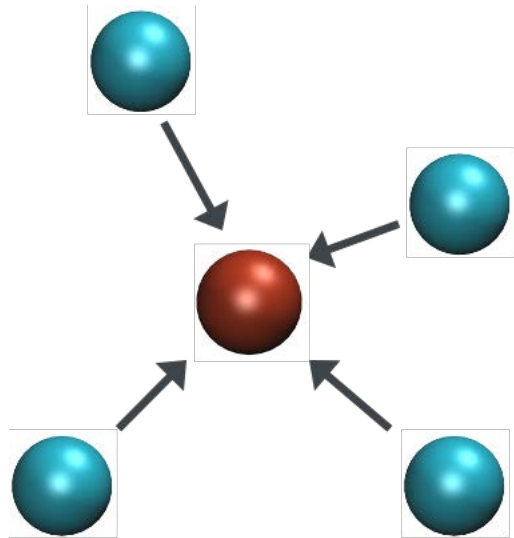
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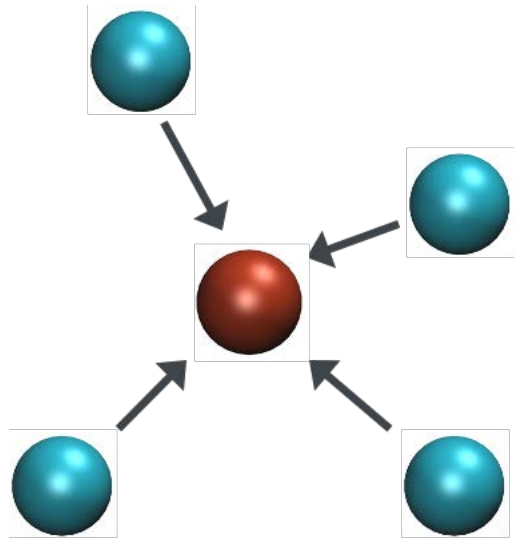
$$U = \sum_{\text{Bond}} k_b (b - b_0)^2 + \sum_{\text{Angle}} k_\theta (\theta - \theta_0)^2 + \sum_{\text{Dihedral}} k_\phi [1 + \cos(n\phi - \delta)] \\ + \sum_{\text{Coulomb}} \frac{q_i q_j}{\epsilon r_{ij}} + \sum_{\text{VdW}} \epsilon \left[\left(\frac{R_{\text{min}_{ij}}}{r_{ij}} \right)^{12} - \left(\frac{R_{\text{min}_{ij}}}{r_{ij}} \right)^6 \right]$$

Basic molecular dynamics simulation algorithm



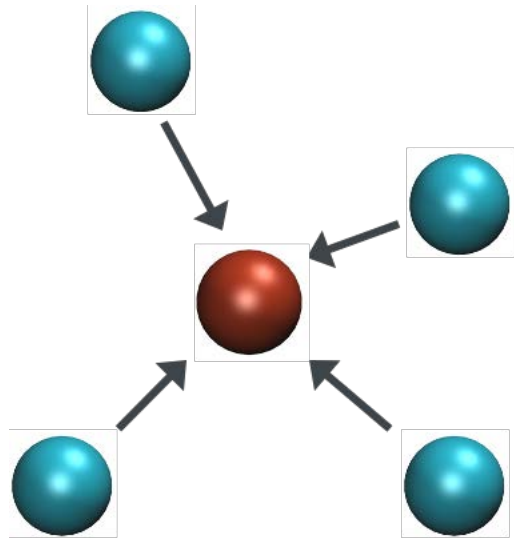
Basic molecular dynamics simulation algorithm

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Basic molecular dynamics simulation algorithm

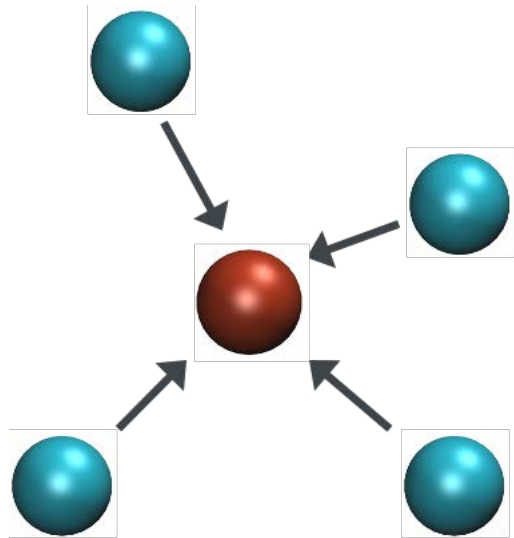
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$$F = \frac{-\partial U(r)}{\partial r}$$

Basic molecular dynamics simulation algorithm

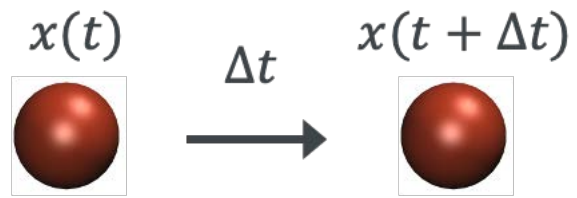
$$U = \sum_{Bond} k_b (b - b_0)^2 + \sum_{Angle} k_\theta (\theta - \theta_0)^2 + \sum_{Dihedral} k_\phi [1 + \cos(n\phi - \delta)] \\ + \sum_{Coulomb} \frac{q_i q_j}{\epsilon r_{ij}} + \sum_{VdW} \epsilon \left[\left(\frac{R_{min_{ij}}}{r_{ij}} \right)^{12} - \left(\frac{R_{min_{ij}}}{r_{ij}} \right)^6 \right]$$



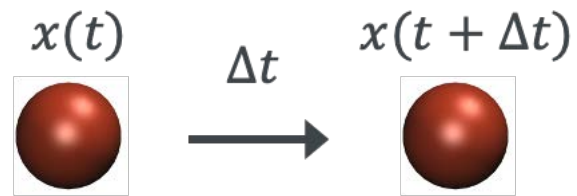
$$F = \frac{-\partial U(r)}{\partial r}$$

$$a = \frac{F}{m}$$

Basic molecular dynamics simulation algorithm



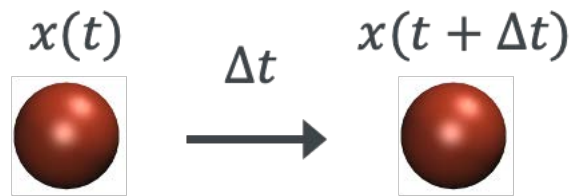
Basic molecular dynamics simulation algorithm



Simple algorithm to propagate system:

- 1) Particle has position $\mathbf{x}$ and velocity $\mathbf{v}$ at time t
- 2) Determine forces and acceleration acting on the particle
- 3) Move the particle for time step Δt

Basic molecular dynamics simulation algorithm



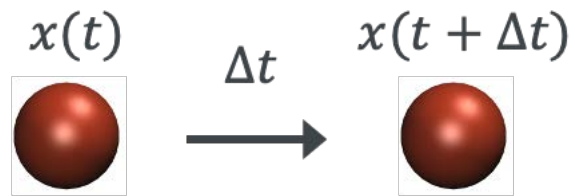
Simple algorithm to propagate system:

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- 3) Move the particle for time step Δt

Update position:

$$x(t + \Delta t) = x(t) + v(t)\Delta t + \frac{1}{2}a(t)\Delta t^2$$

Basic molecular dynamics simulation algorithm



Simple algorithm to propagate system:

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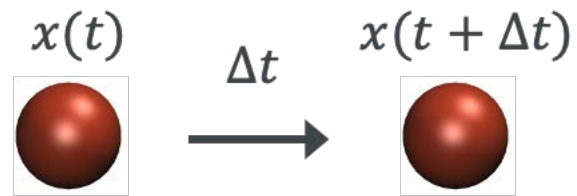
Update position:

$$x(t + \Delta t) = x(t) + v(t)\Delta t + \frac{1}{2}a(t)\Delta t^2$$

Update velocity:

$$v(x + \Delta t) = \frac{x(t + \Delta t) - x(t)}{\Delta t}$$

Basic molecular dynamics simulation algorithm



Simple algorithm to propagate system:

- 1) Particle has position $\mathbf{x}$ and velocity $\mathbf{v}$ at time t
- 2) Determine forces and acceleration acting on the particle
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Update position:

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Update velocity:

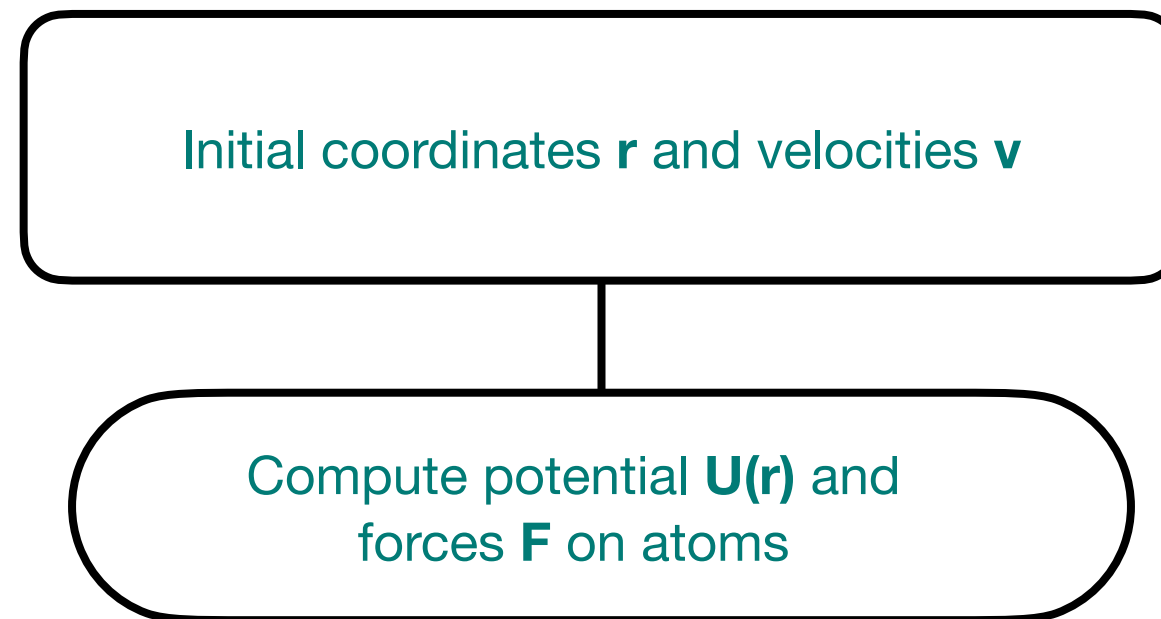
$$v(x + \Delta t) = \frac{x(t + \Delta t) - x(t)}{\Delta t}$$

How small/large can Δt be?

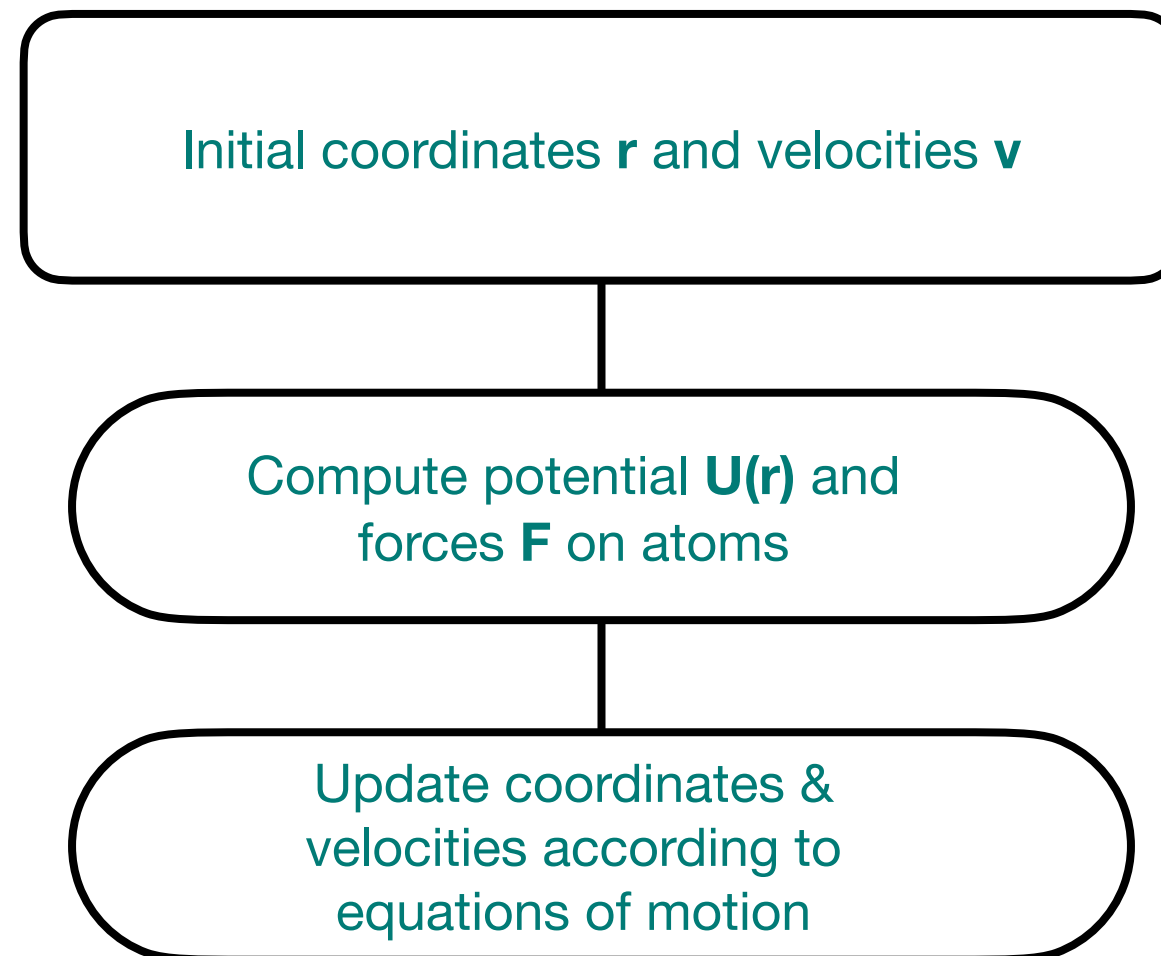
Molecular dynamics simulations: Algorithm

Initial coordinates $\mathbf{r}$ and velocities $\mathbf{v}$

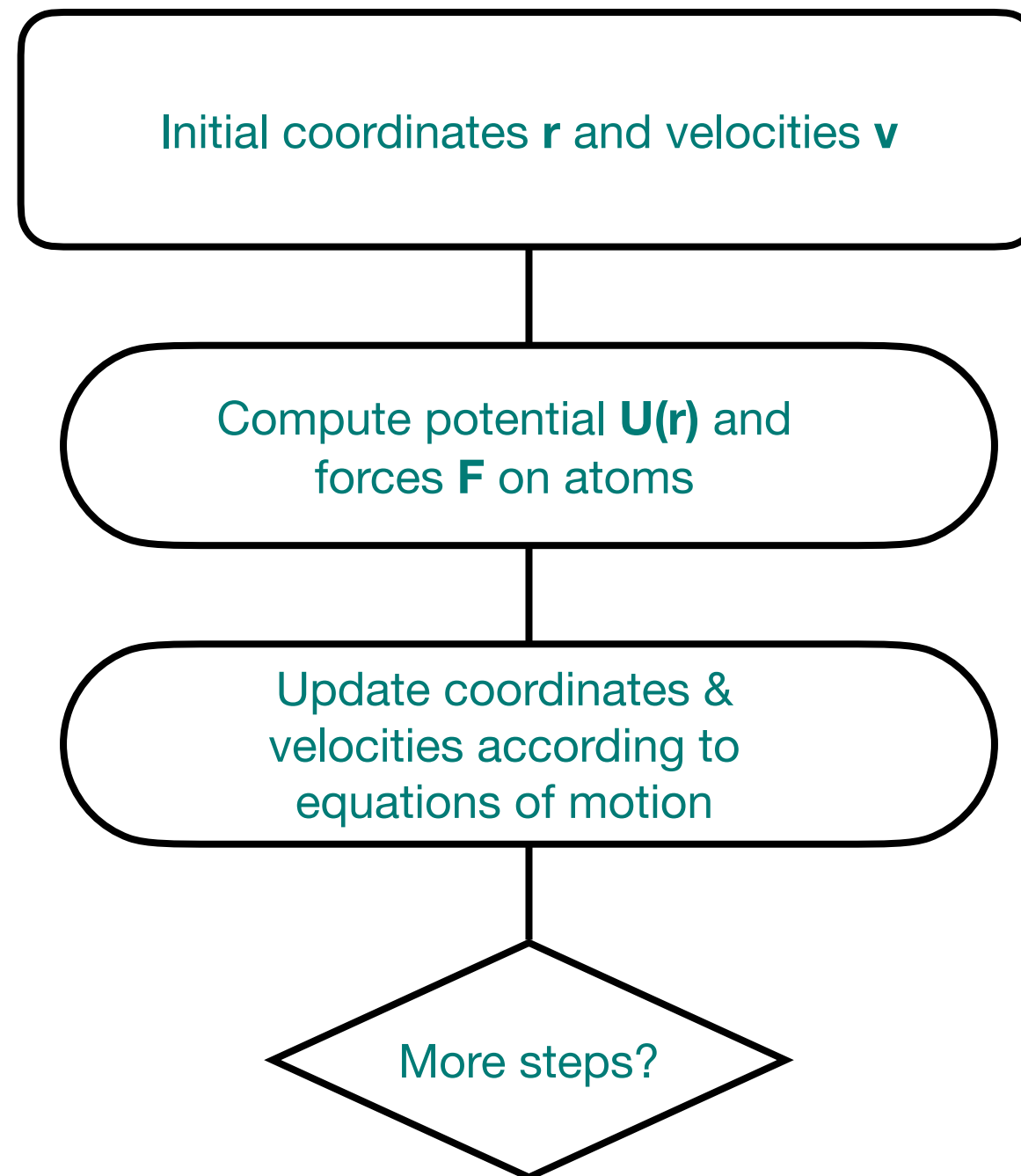
Molecular dynamics simulations: Algorithm



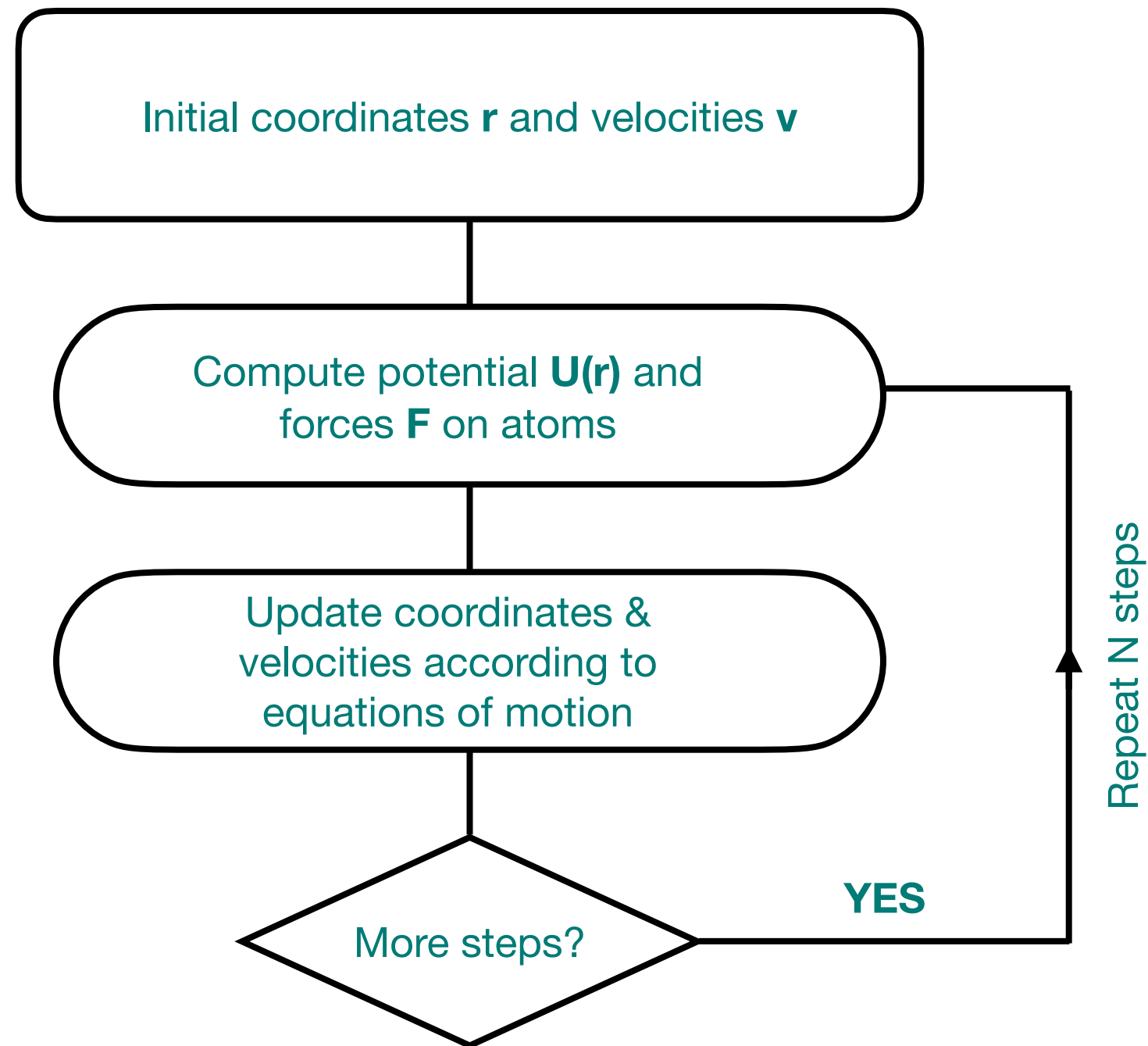
Molecular dynamics simulations: Algorithm



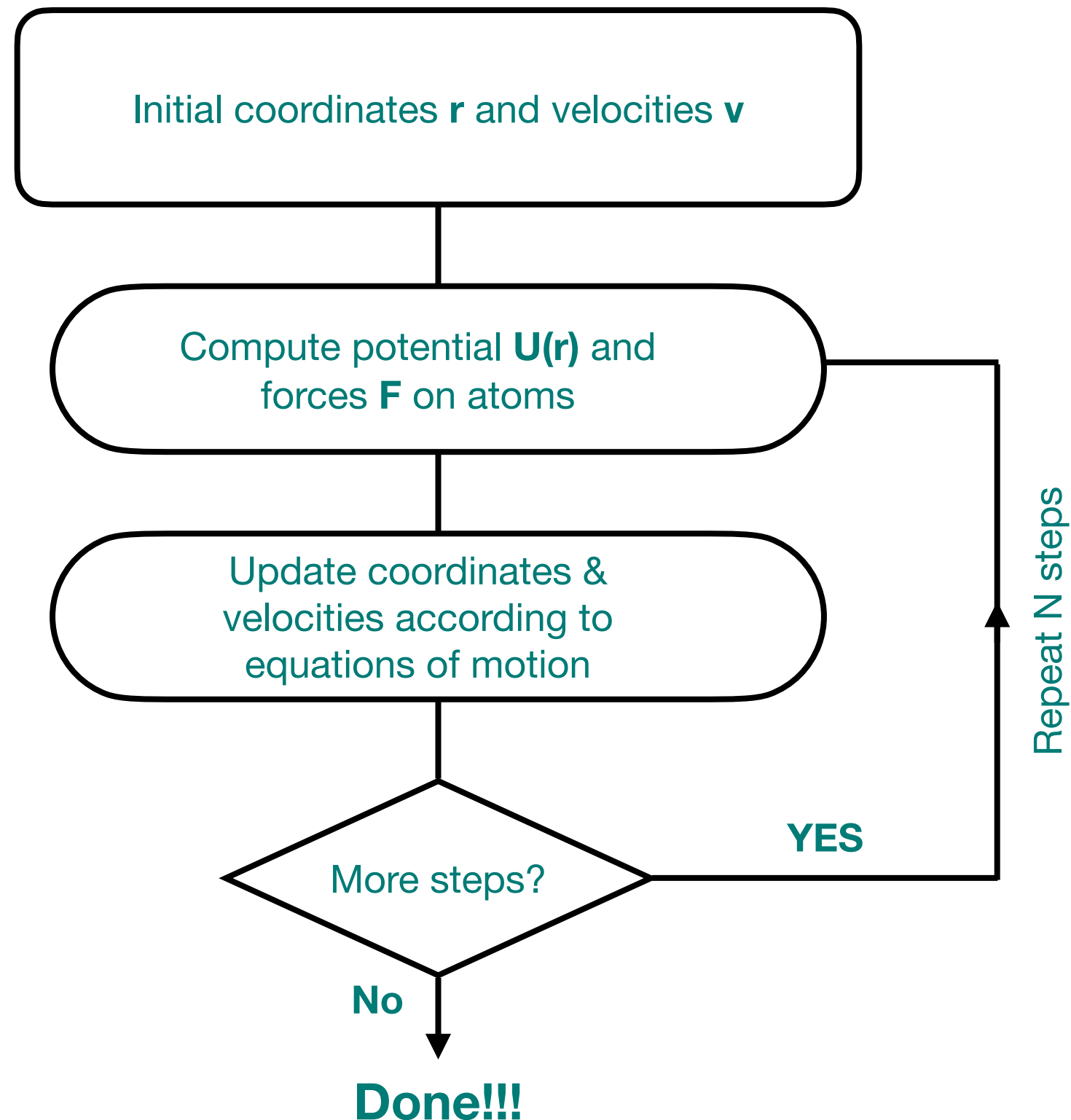
Molecular dynamics simulations: Algorithm



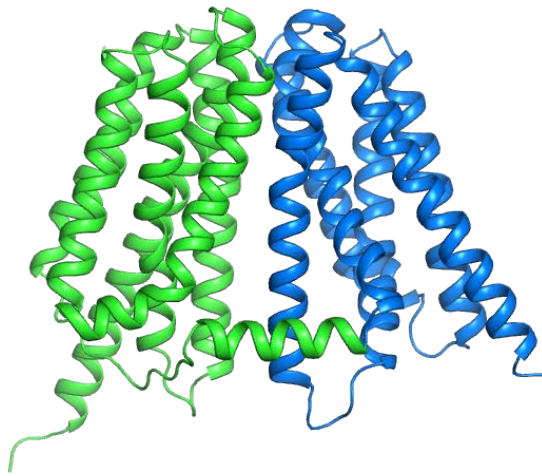
Molecular dynamics simulations: Algorithm



Molecular dynamics simulations: Algorithm

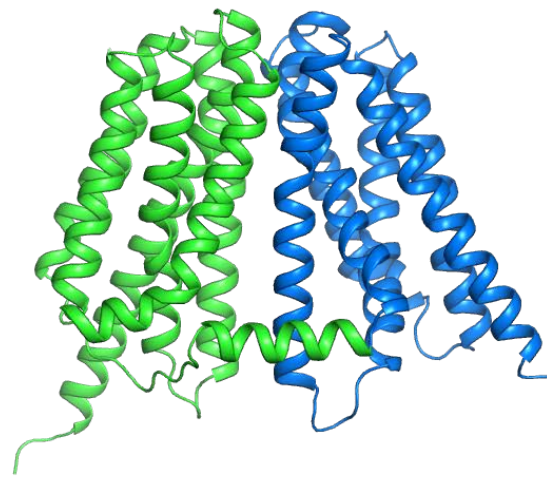


How to run an MD simulation?



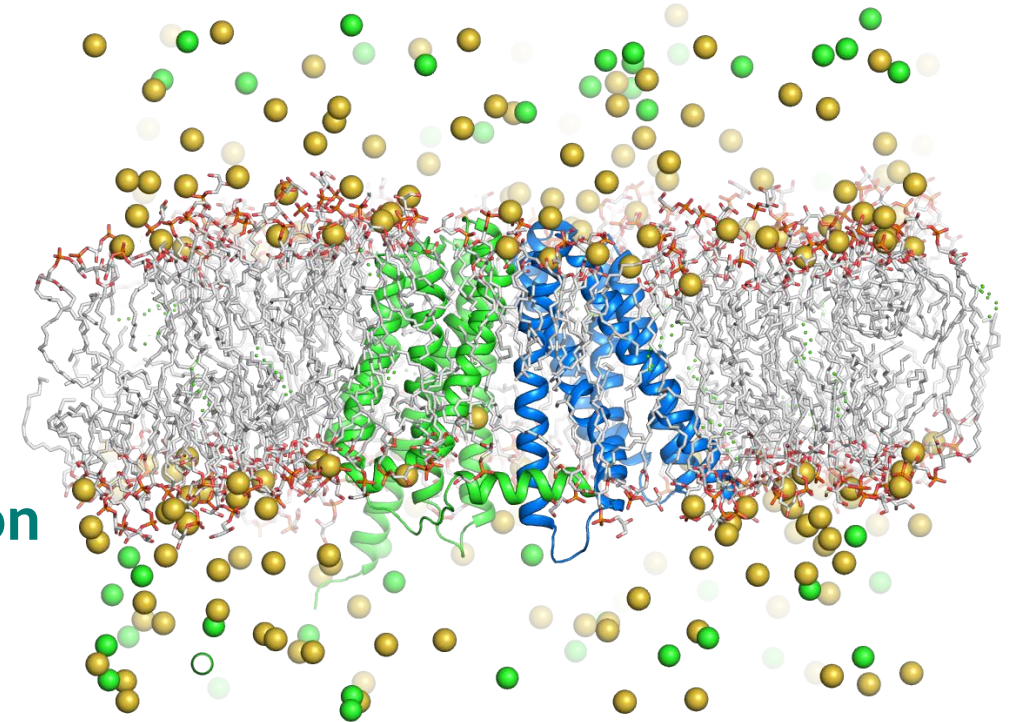
Protein preparation

How to run an MD simulation?

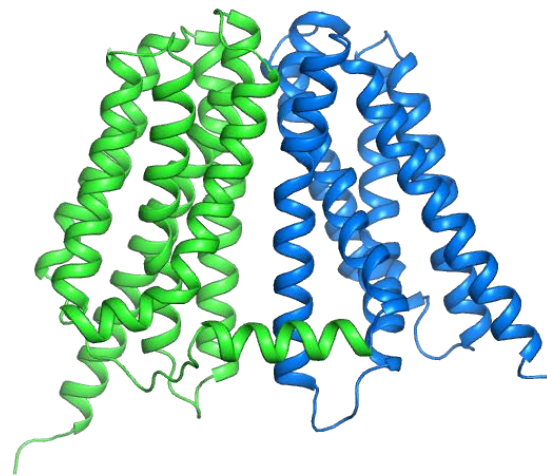


Protein preparation

Add membrane
→
And ions
to reach physiological concentration

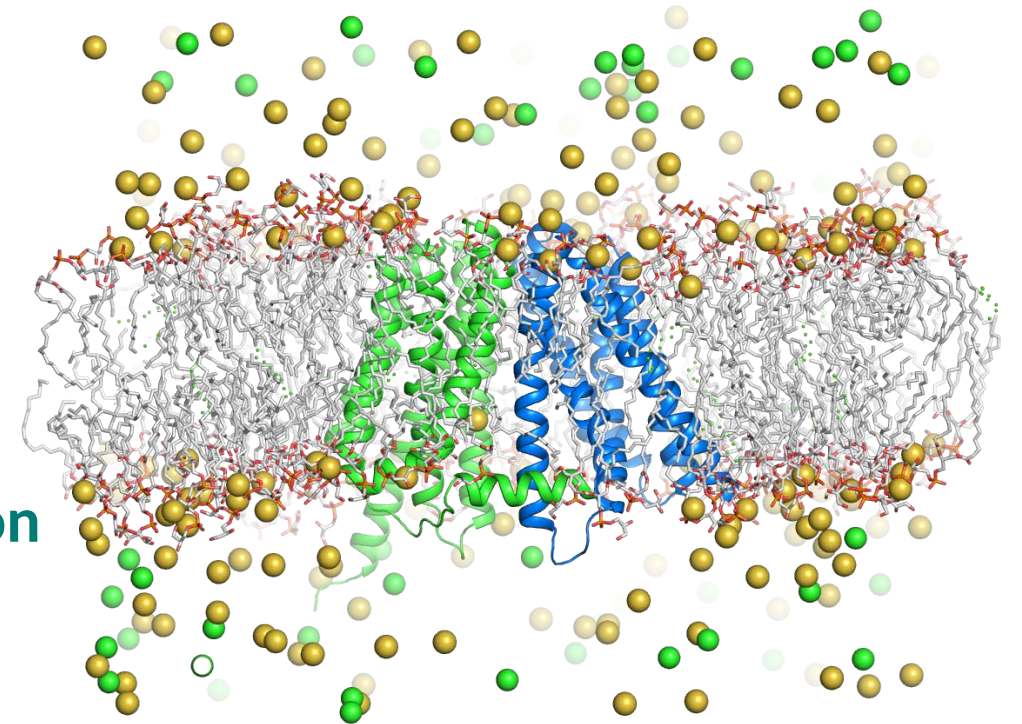


How to run an MD simulation?

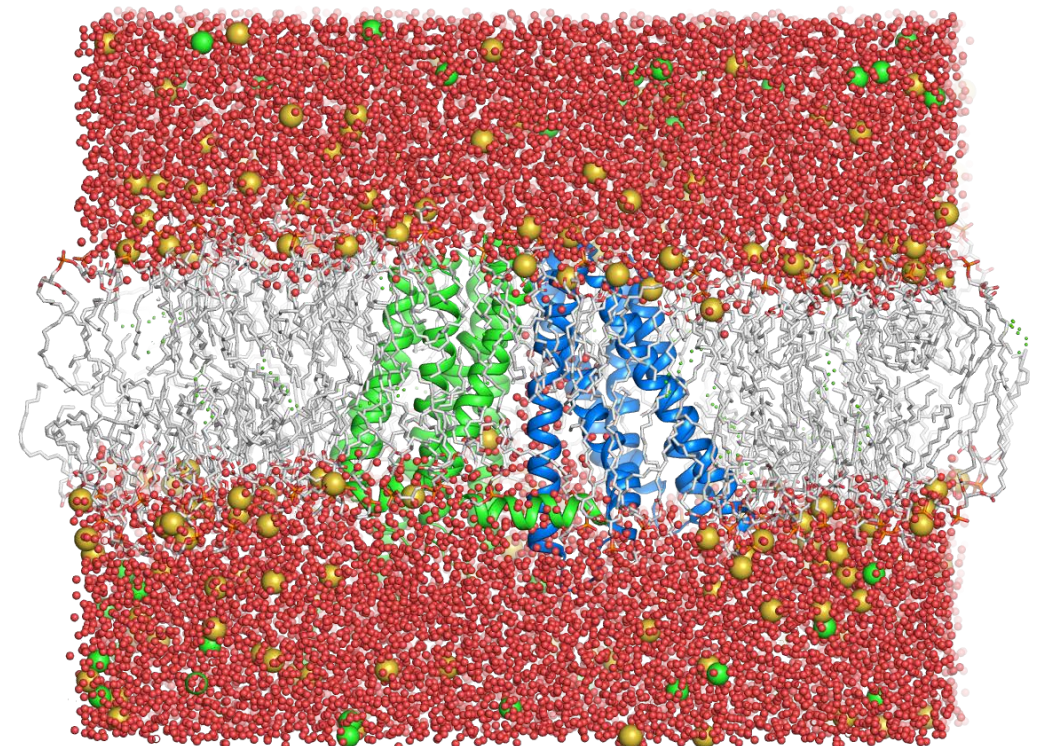


Protein preparation

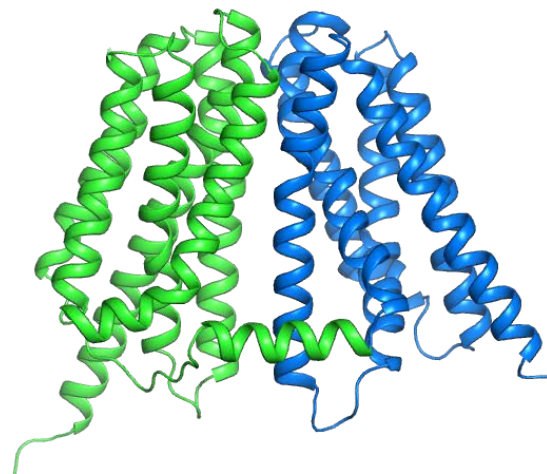
Add membrane
→
And ions
to reach physiological concentration



↓ Add water

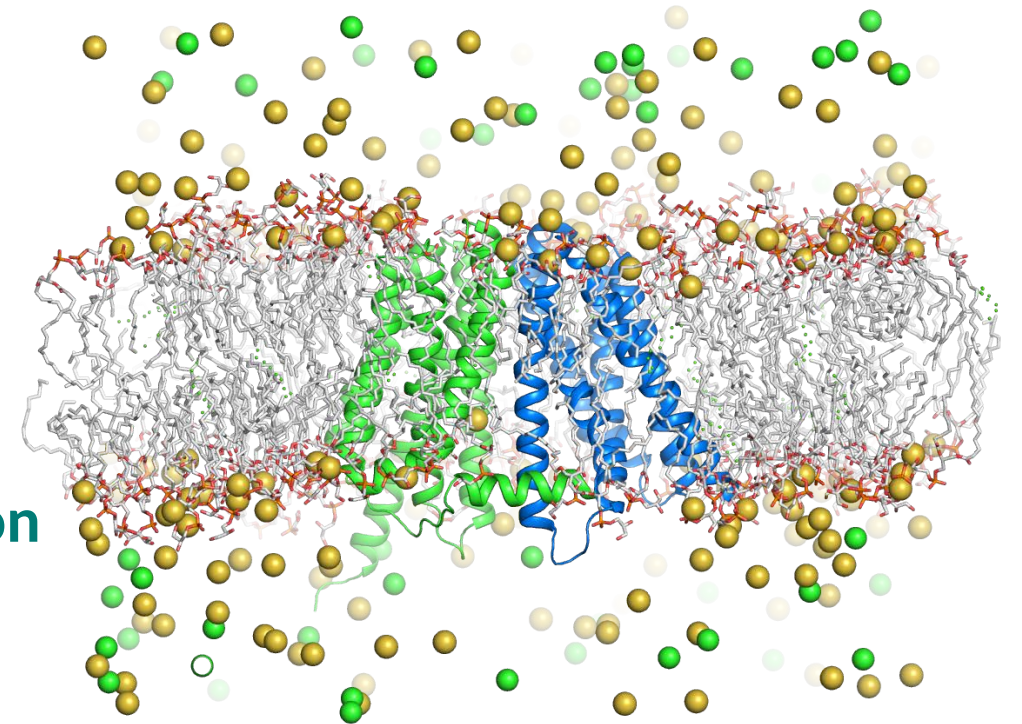


How to run an MD simulation?

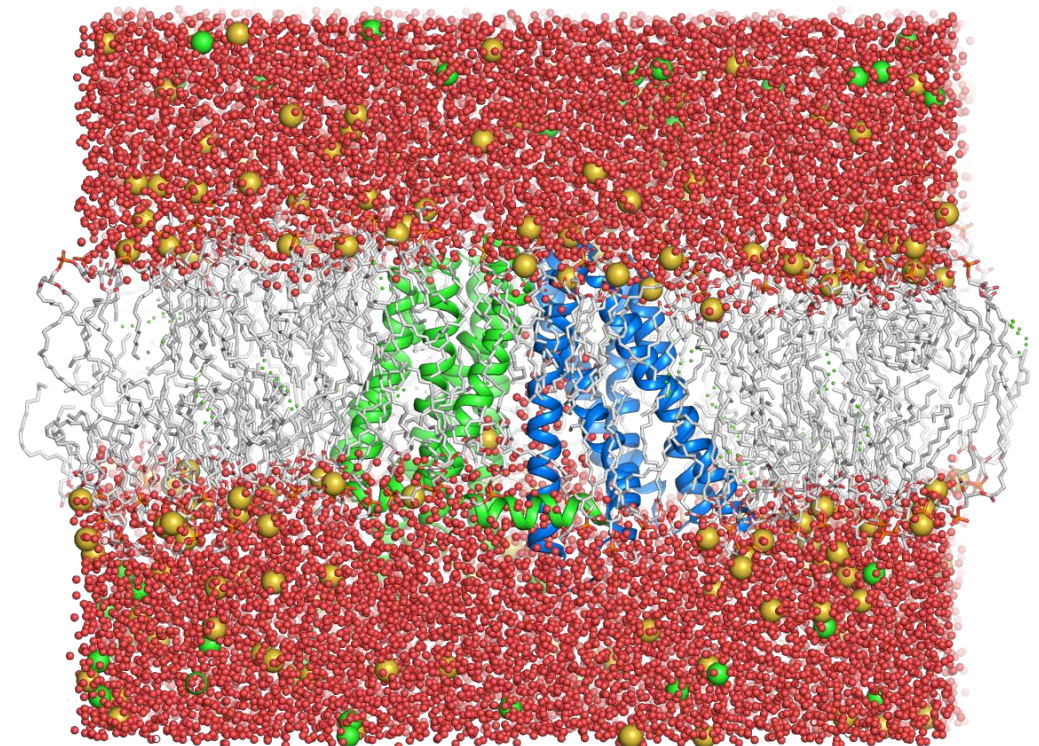


Protein preparation

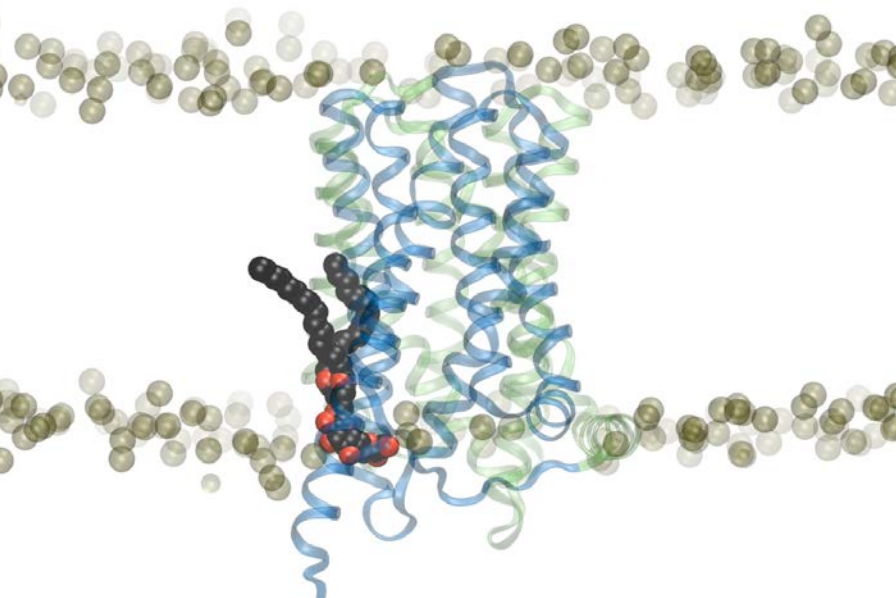
Add membrane
And ions
to reach physiological concentration



Add water



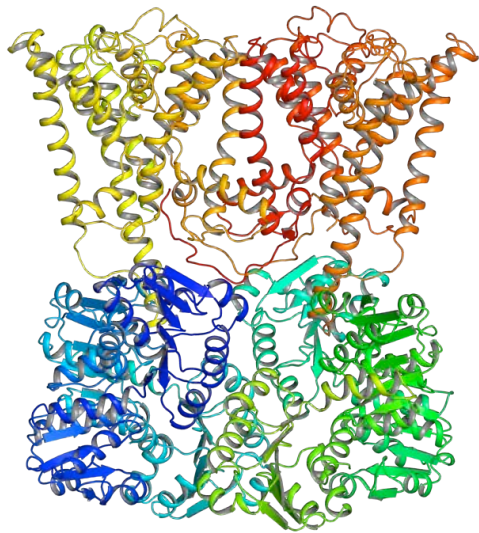
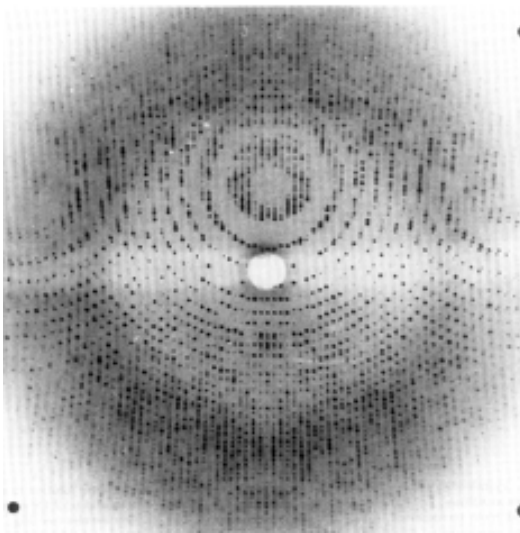
Run the simulation



Membrane protein structure as starting point

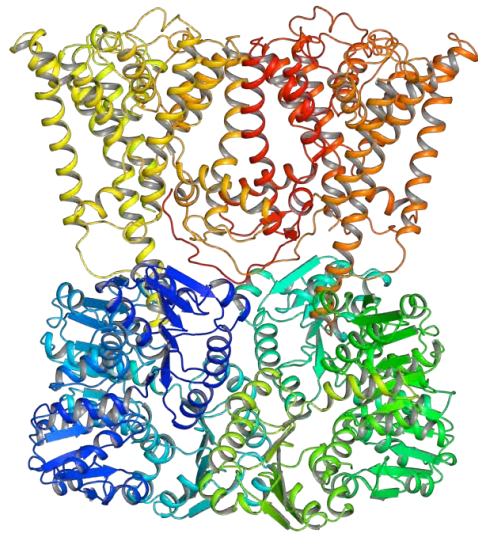
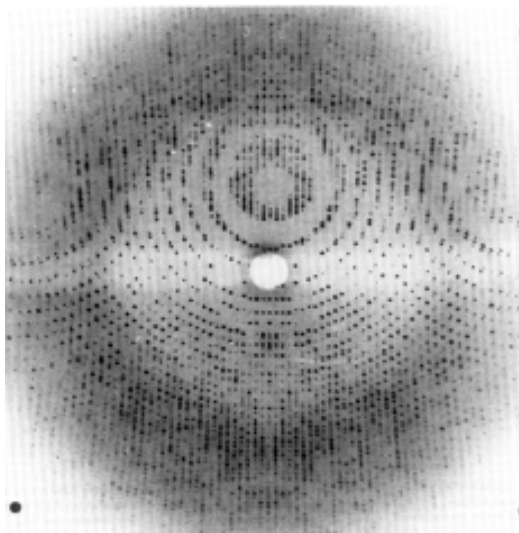
Membrane protein structure as starting point

X-ray crystallography

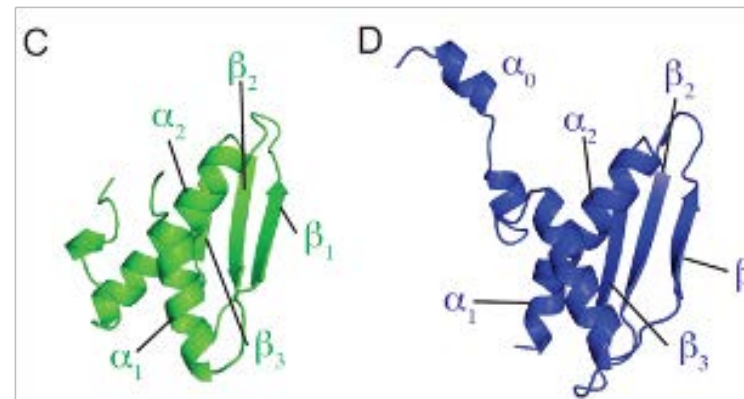


Membrane protein structure as starting point

X-ray crystallography

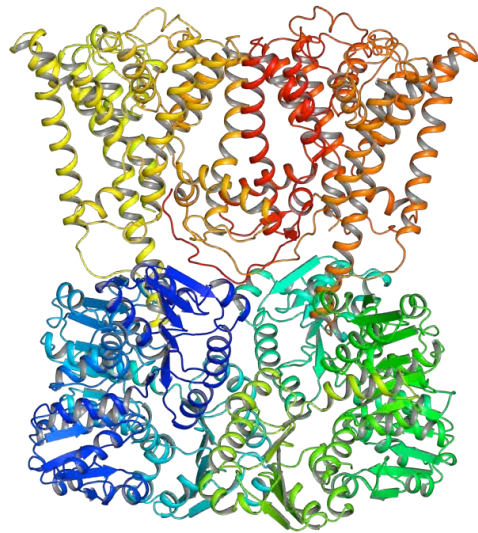
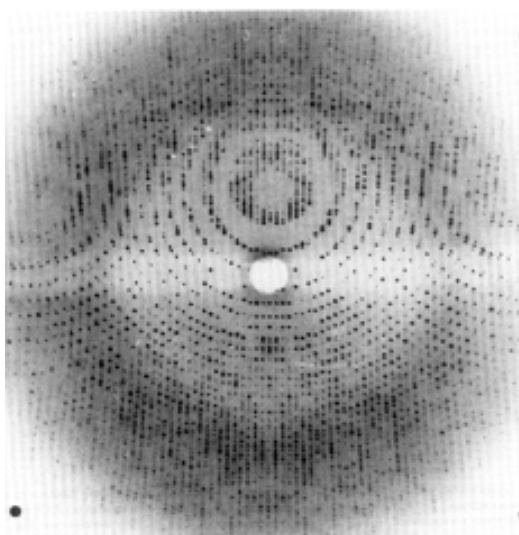


NMR

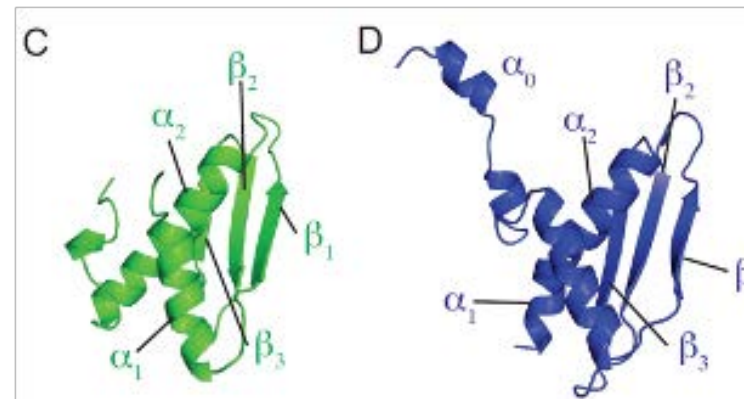


Membrane protein structure as starting point

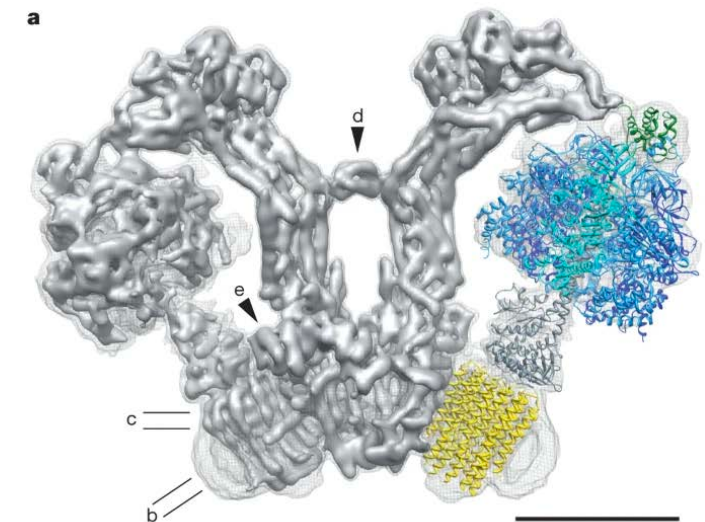
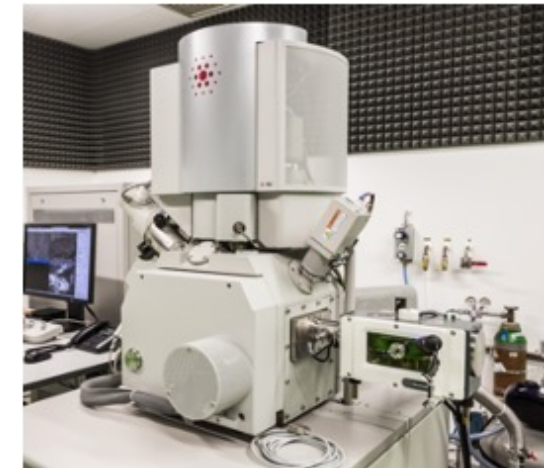
X-ray crystallography



NMR

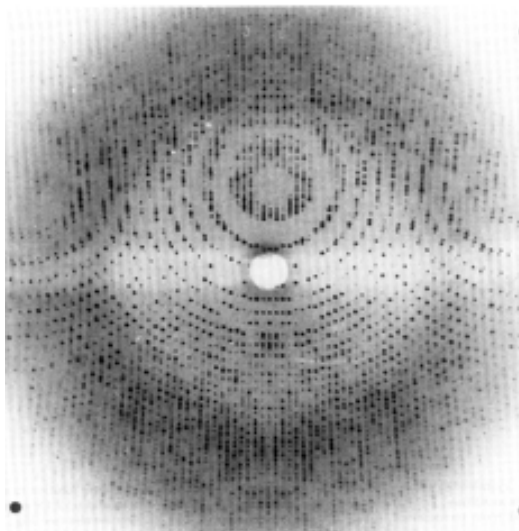


Cryo-EM



Membrane protein structure as starting point

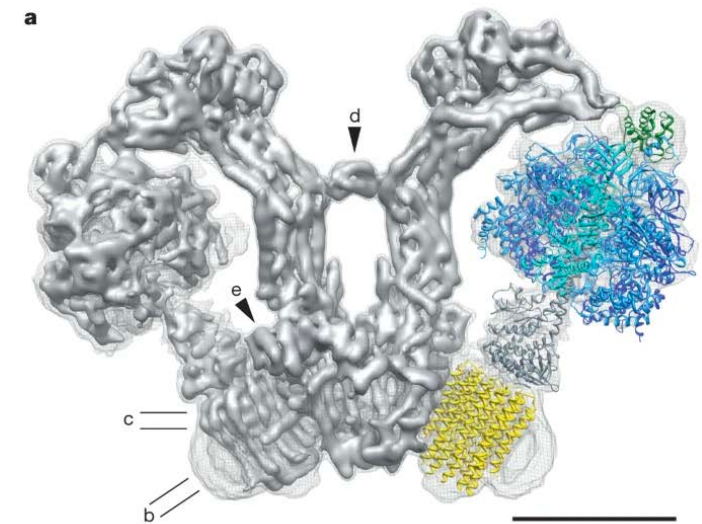
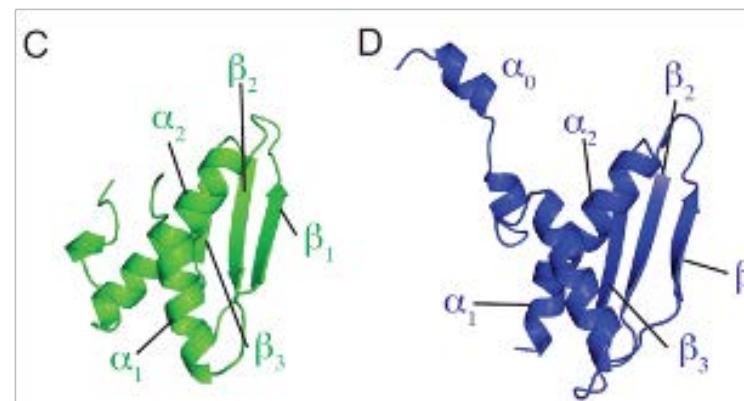
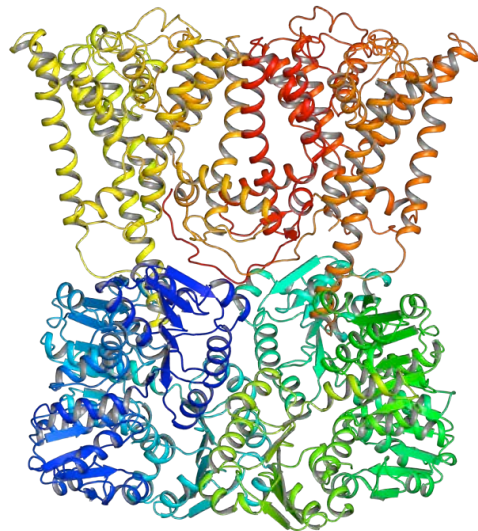
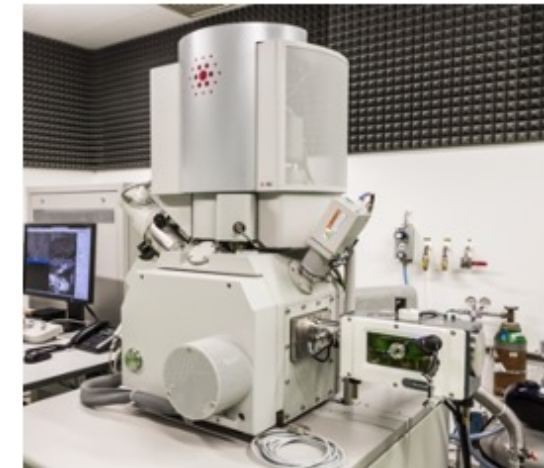
X-ray crystallography



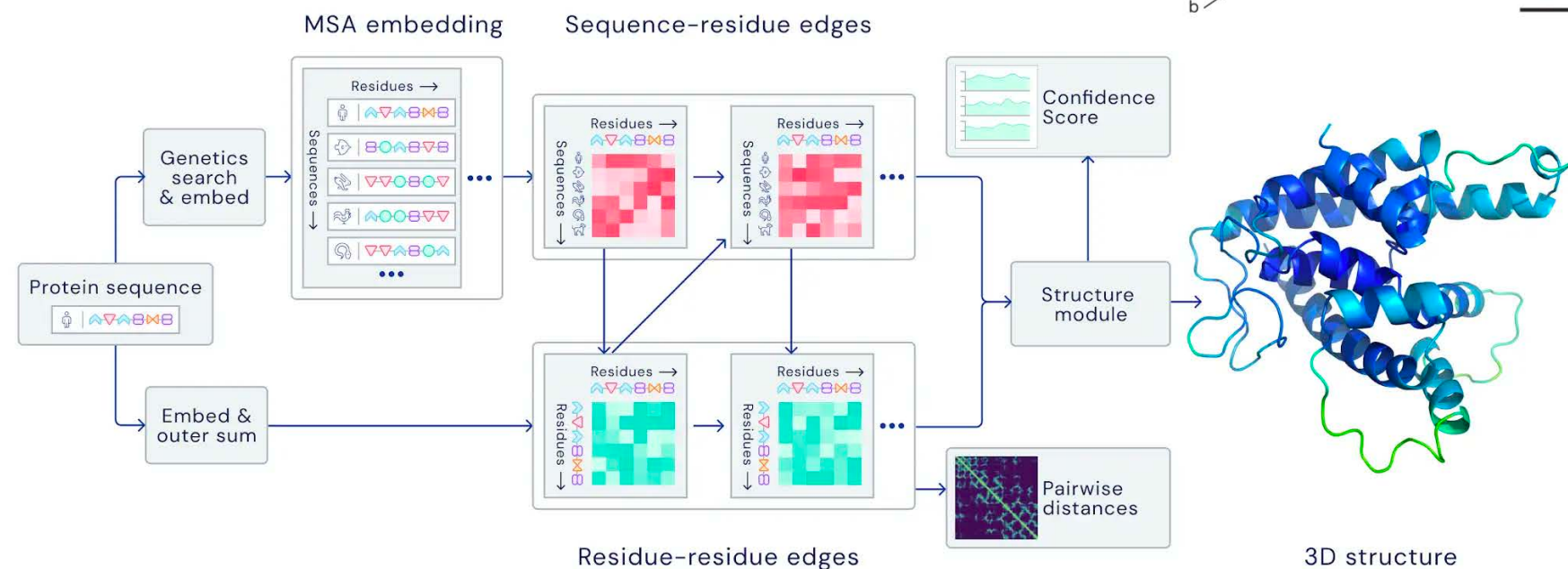
NMR



Cryo-EM

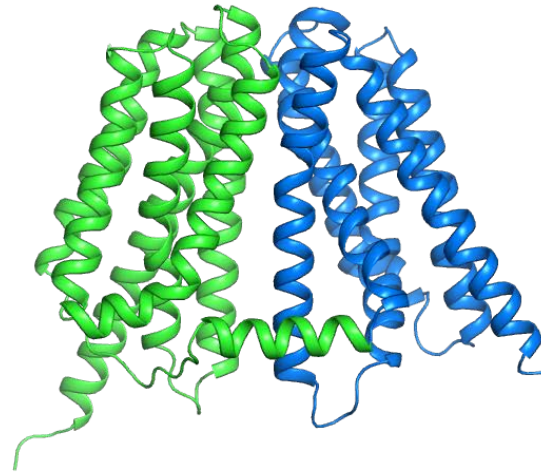


ML/AI-based
structure prediction



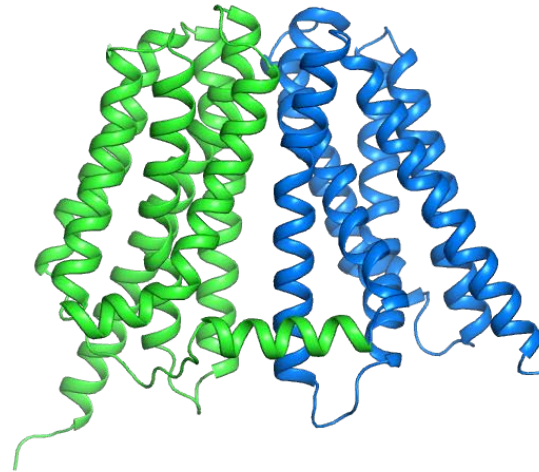
Protein preparation

Protein preparation



Protein preparation

Protein preparation

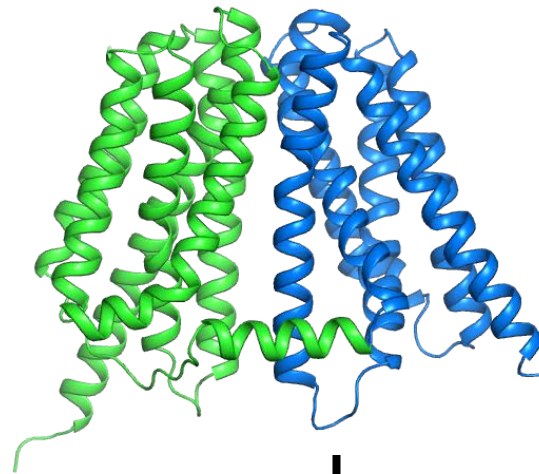


Structure refinement:

1. Add missing side-chains
2. Add missing loop

Protein preparation

Protein preparation



Structure refinement:

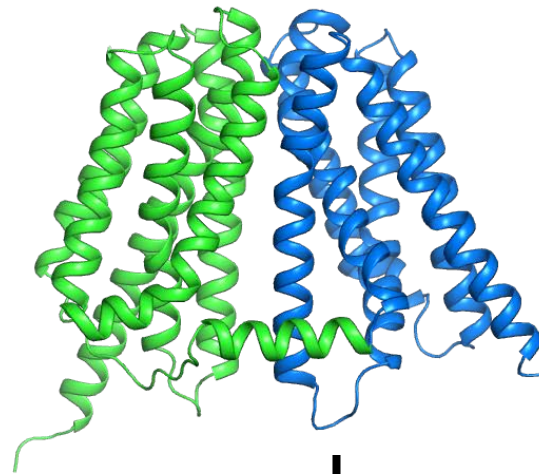
1. Add missing side-chains
2. Add missing loop

Add hydrogen atoms

1. Titrable residues?
2. pKa calculations

Protein preparation

Protein preparation



Structure refinement:

1. Add missing side-chains
2. Add missing loop

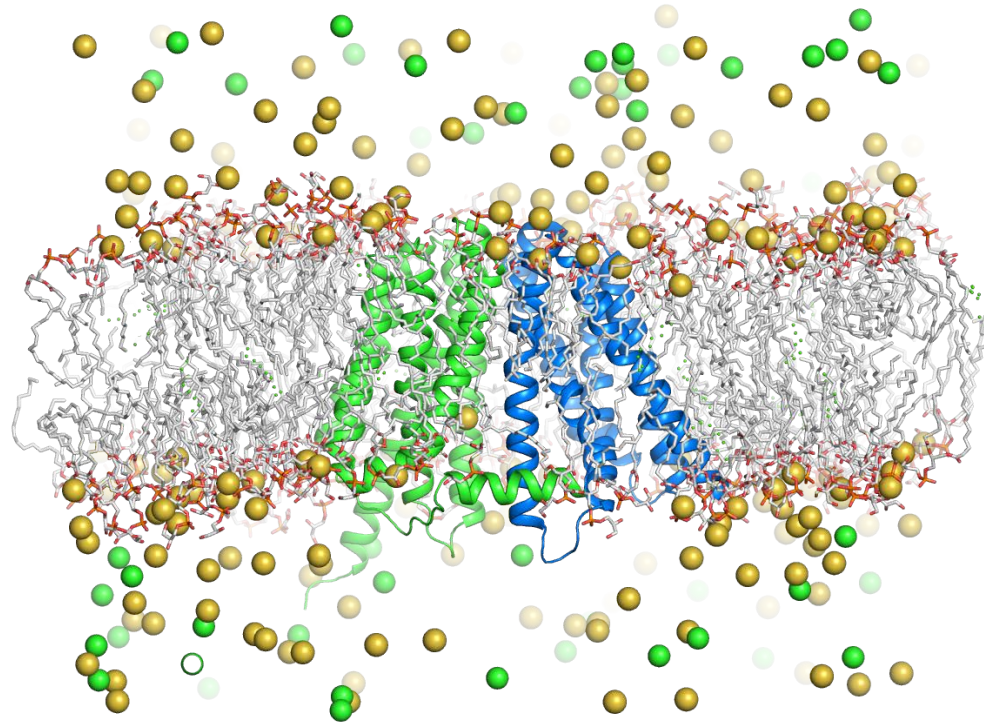
Add hydrogen atoms

1. Titrable residues?
2. pKa calculations

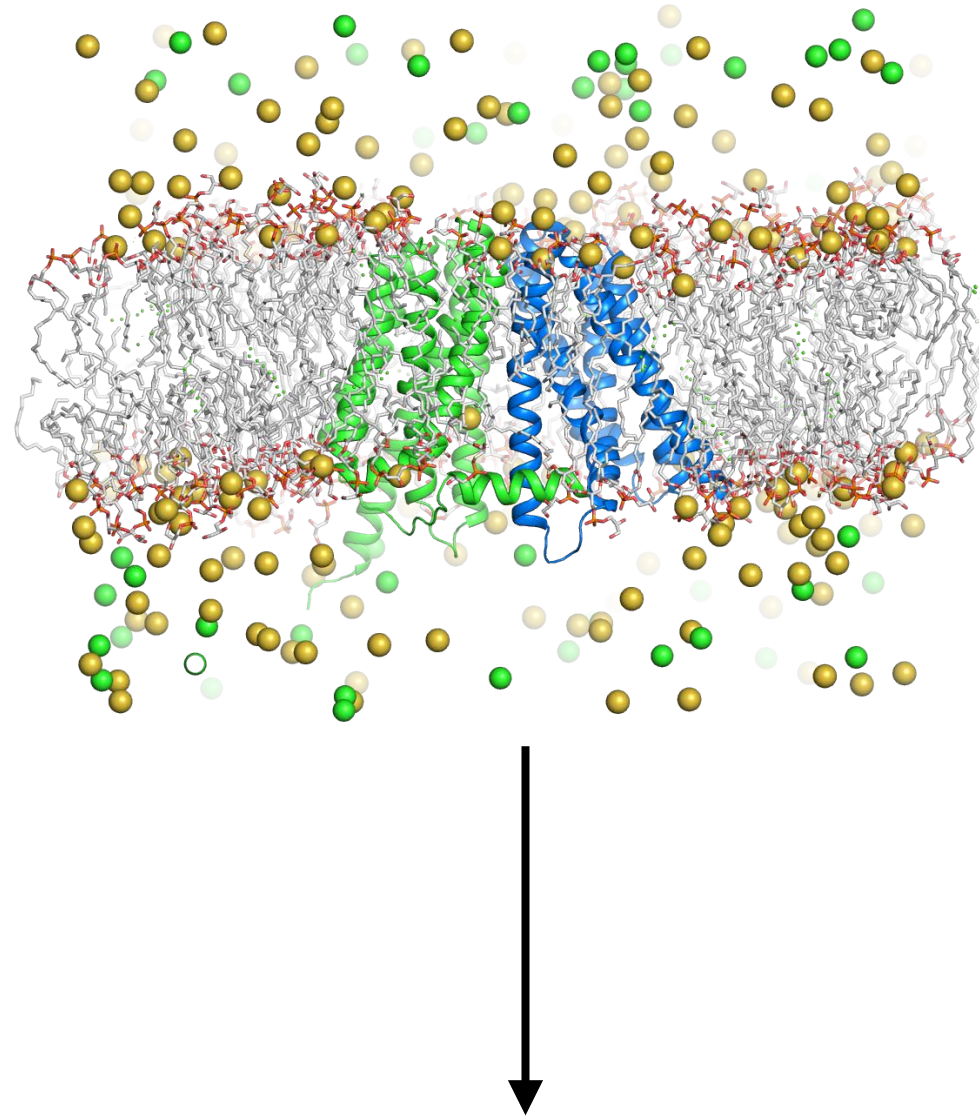
Structure minimisation:

1. Removing steric clashes

Add membrane



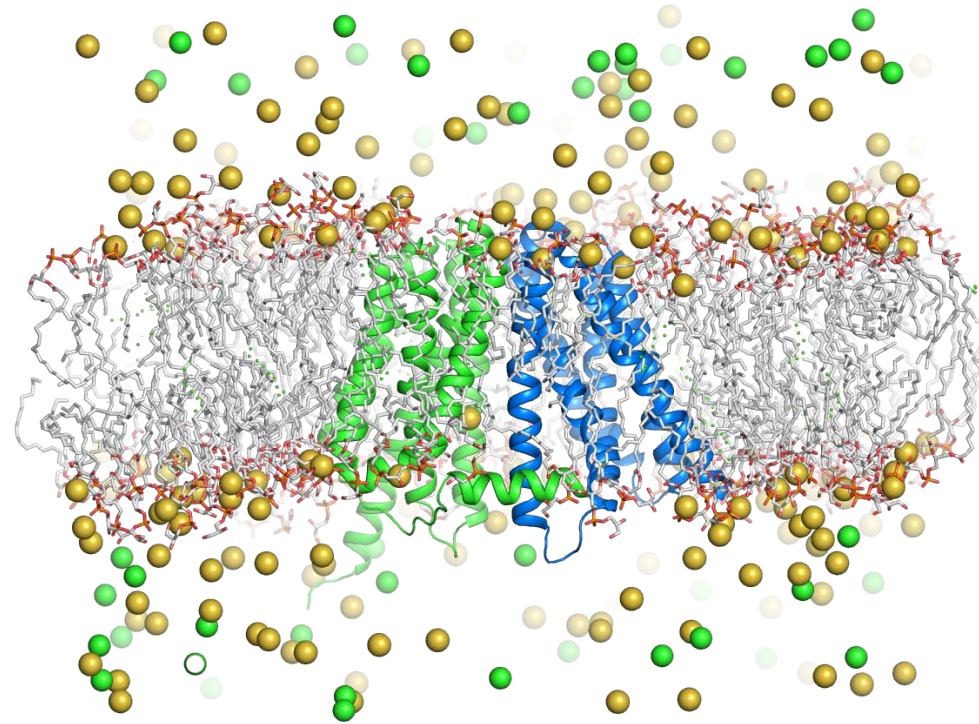
Add membrane



Complexity of membrane composition

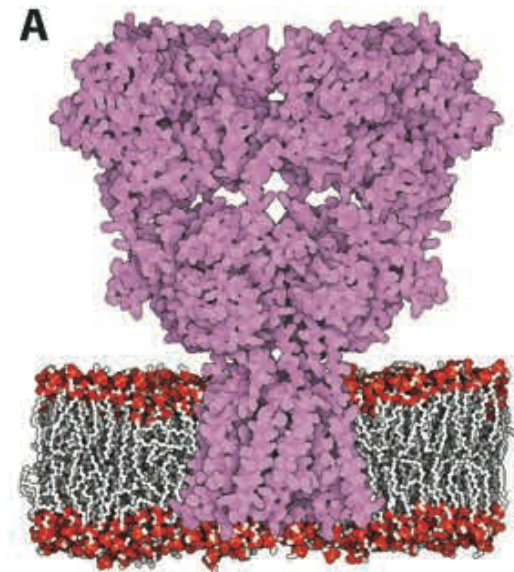
1. Homogenous membrane
2. Heterogeneous membrane

Add membrane

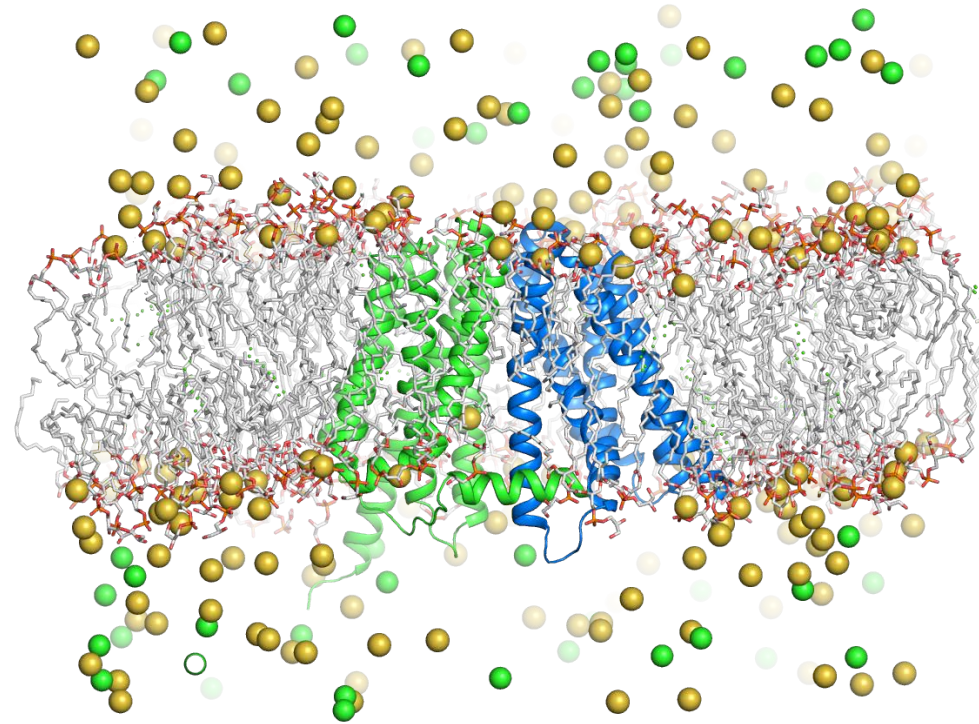


Complexity of membrane composition

1. Homogenous membrane
2. Heterogeneous membrane

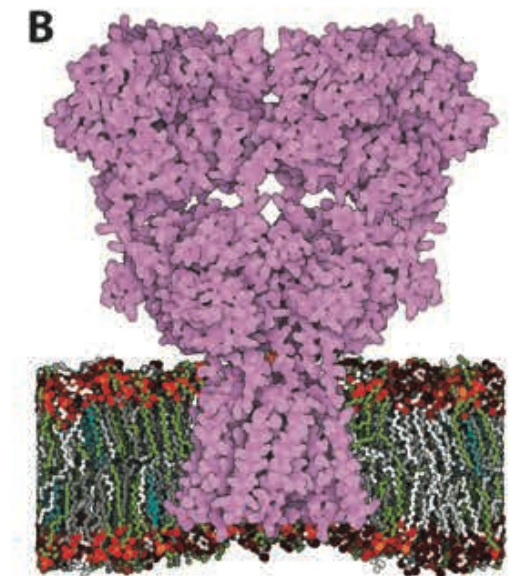
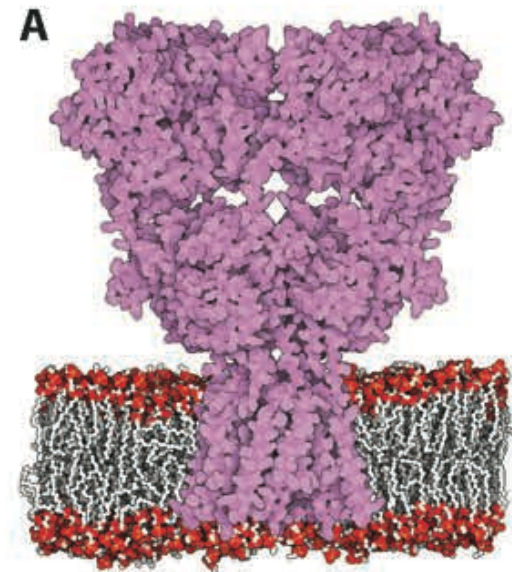


Add membrane



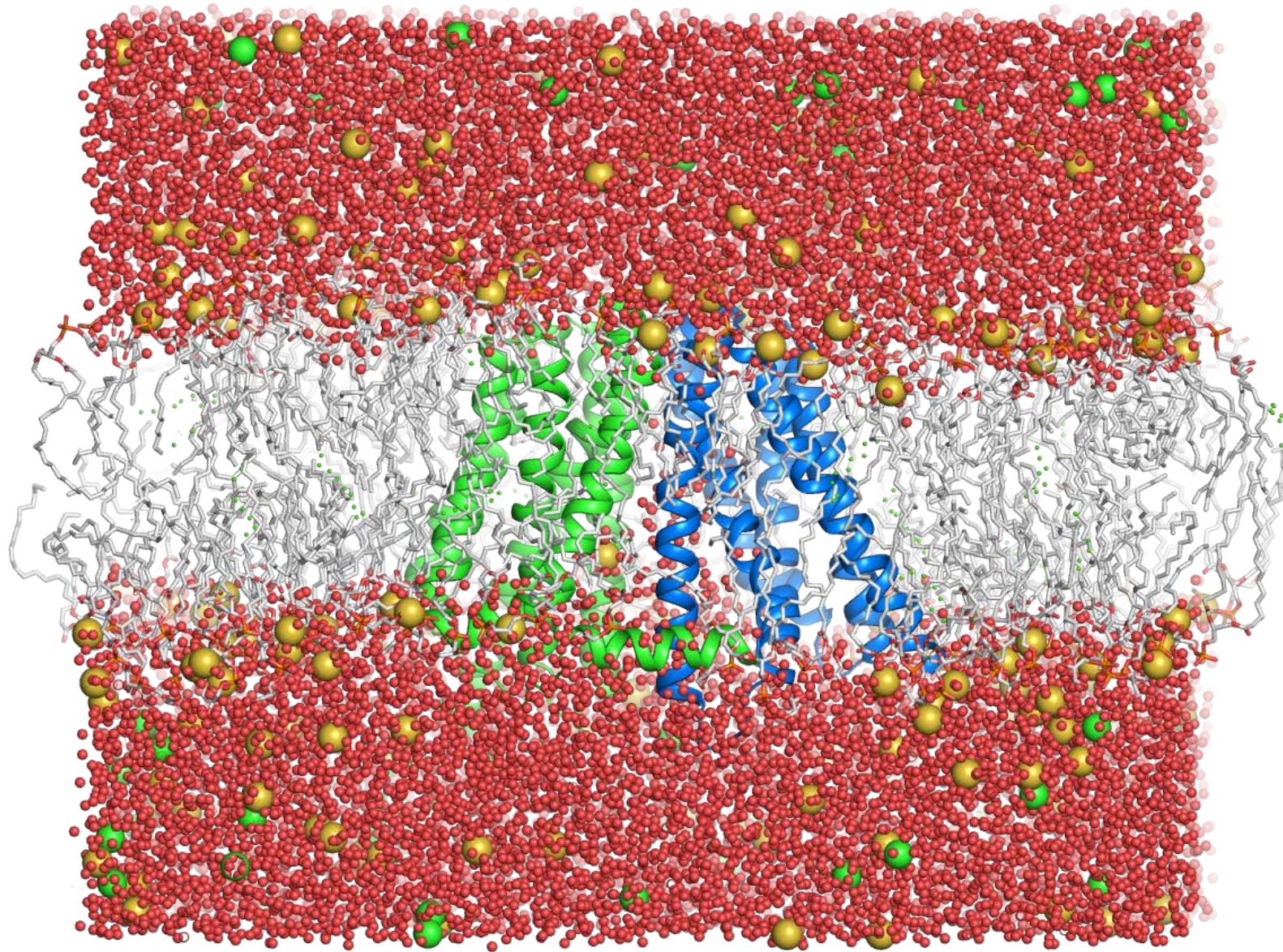
Complexity of membrane composition

1. Homogenous membrane
2. Heterogeneous membrane



Add water: full system

Add water: full system



Engines to run MD

openmm/openmm

OpenMM is a toolkit for molecular simulation using high performance GPU code.



NAMD
Scalable Molecular Dynamics

GROMACS
fast, flexible & free



AMBER MD

Molecular Dynamics Simulations
HARMM

A web-server to setup your system

CHARMM-GUI
Effective Simulation Input Generator and More

CHARMM is a versatile program for atomic-level simulation of many-particle systems, particularly macromolecules of biological interest. - M. Karplus

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Front Page

Since its original development in 2006, CHARMM-GUI has proven to be an ideal web-based platform to interactively build complex systems and prepare their inputs with well-established and reproducible simulation protocols for state-of-the-art molecular simulations using widely used simulation packages such as CHARMM, NAMD, GROMACS, AMBER, GENESIS, Tinker, LAMMPS, Desmond, and OpenMM. The CHARMM-GUI development project has been widely adopted for various purposes and now contains a number of different modules designed to set up a broad range of molecular simulation systems in [Input Generator](#). Many original modules were developed as an in-house effort, but we have established close collaborations with the developers of CHARMM and other MD simulation packages for addition of newer modules.

Our philosophy in CHARMM-GUI development is less about providing the nuts and bolts of molecular modeling, but instead focused on helping users to achieve a task, such as building a membrane system or solvating a protein, by providing a streamlined interface. This design principle helps us to think of the workflow critically when designing the interface, which leads CHARMM-GUI to be accessible to users with little experience in modeling tools and remains useful to experts, especially for batch generation of systems. CHARMM-GUI has been used by many researchers, and it is a well-recognized tool in the molecular modeling and simulation communities (see [Google Scholar Citations](#)).

The CHARMM-GUI development project is still ongoing. These functionalities are not only based on requests from general users and developers, but also on an emerging need for a unified platform to prepare and execute various advanced simulation approaches that have been developed and will be developed by many developers in diverse simulation communities and packages. CHARMM-GUI will continue to help expert and non-expert researchers from a broader range of the modeling and simulation community to build the complex molecular systems of their interest and prepare the input files for any general and advanced modeling and simulation through the large and unique scope of CHARMM-GUI functionality. It will also provide an effective one-stop online resource for the biomedical research community to carry out innovative and novel molecular modeling and simulation research.

Visit our [COVID-19 Archive](#) for collection of SARS-CoV-2 protein systems.
Follow CHARMM-GUI on Twitter: <https://twitter.com/CharmmGui>.

Geographical Visitors

LEHIGH
UNIVERSITY

Lehigh University / Department of Biological Sciences / Department of Chemistry / Department of Bioengineering / Im Lab
Problems, Questions, & Comments? [E-Mail](#) / [Forum](#) / Copyright(c) 2006-2022 by the Im Lab

A web-server to setup your system

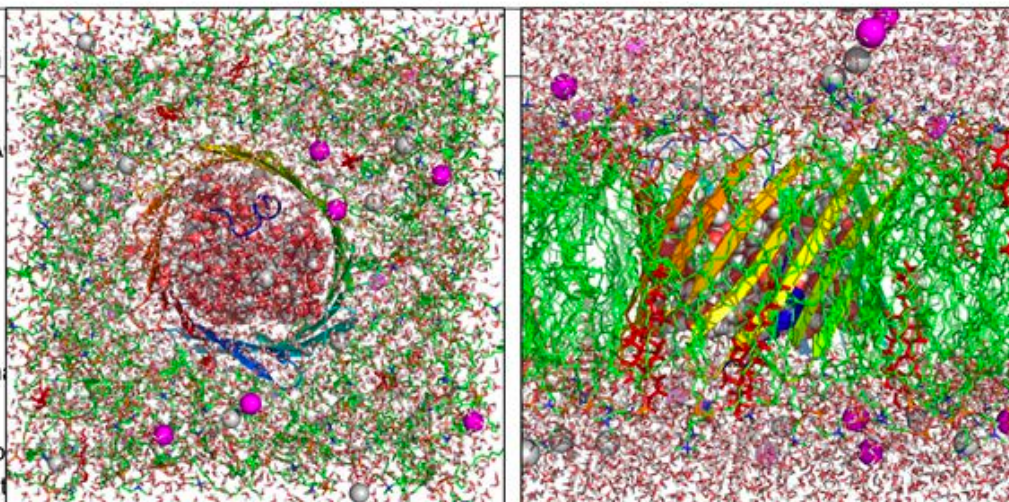
Membrane Builder

Bookmark this [link](#), if you want to comeback to this page

PDB Info	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6
Lipid PDB:	step4_lipid.pdb (view structure)					download .tgz
Assembly Input:	step5_assembly.inp					
Assembly Output:	step5_assembly.out					
System Information:	step5_assembly.str					
Assembled PSF:	step5_assembly.psf					
XPLOR PSF:	step5_assembly.xplor.psf					
Assembled CRD:	step5_assembly.crd					
Assembled PDB:	step5_assembly.pdb (view structure)					

Determined System

of Atoms
Crystal Type TETRA
System Size A
B
C
Crystal Angle Alpha
Beta
Gamma
Lipid POPC
of Lipids on Top
on Bottom
of Water 7205
of POT Ion 19
of CLA Ion 21
Z Center -1.8245



Assembled structure of protein/membrane complex. Spheres represents potassium (magenta) and chloride (gray) ions. Pore water molecules are represented as spheres as well (red and white). Cholesterols are colored in red.

Center of the system along the Z axis

Equilibration Options:

- ☒ Generate grid information for PME FFT automatically
☐ Explicit grid information for PME FFT

X Y Z
☐ ☐ ☐

- ☒ NPAT ensemble
☐ NPgT ensemble

Surface Tension (dyne/cm)

Temperature: K

A web-server to setup your system

Membrane Builder

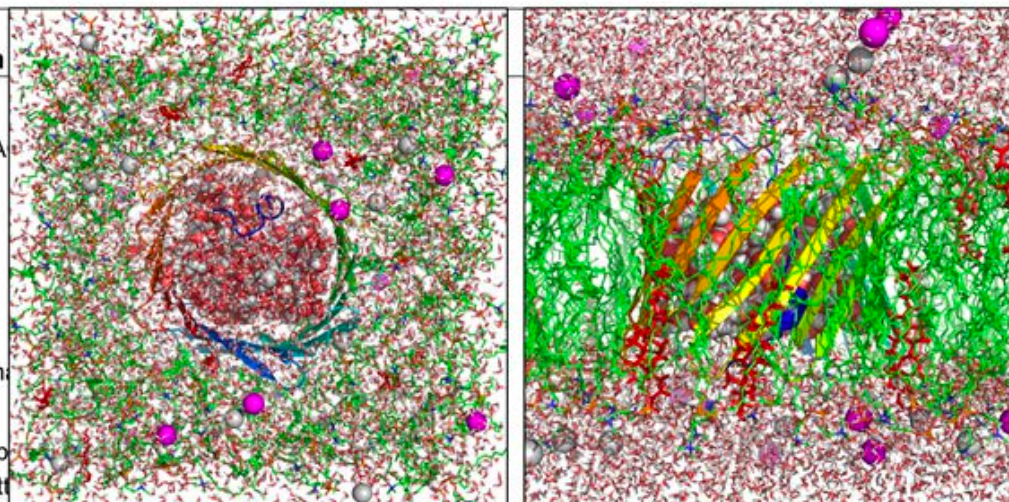
Bookmark this [link](#), if you want to comeback to this page

PDB Info STEP 1 STEP 2 STEP 3 STEP 4 **STEP 5** STEP 6

Lipid PDB: [step4_lipid.pdb \(view structure\)](#) [download .tgz](#)
Assembly Input: [step5_assembly.inp](#)
Assembly Output: [step5_assembly.out](#)
System Information: [step5_assembly.str](#)
Assembled PSF: [step5_assembly.psf](#)
XPLOR PSF: [step5_assembly.xplor.psf](#)
Assembled CRD: [step5_assembly.crd](#)
Assembled PDB: [step5_assembly.pdb \(view structure\)](#)

Determined System

of Atoms
Crystal Type TETRA
System Size A
B
C
Crystal Angle Alpha
Beta
Gamma
Lipid POPC
of Lipids on Top
on Bottom
of Water 7205
of POT Ion 19
of CLA Ion 21
Z Center -1.8245



Assembled structure of protein/membrane complex. Spheres represents potassium (magenta) and chloride (gray) ions. Pore water molecules are represented as spheres as well (red and white). Cholesterols are colored in red.

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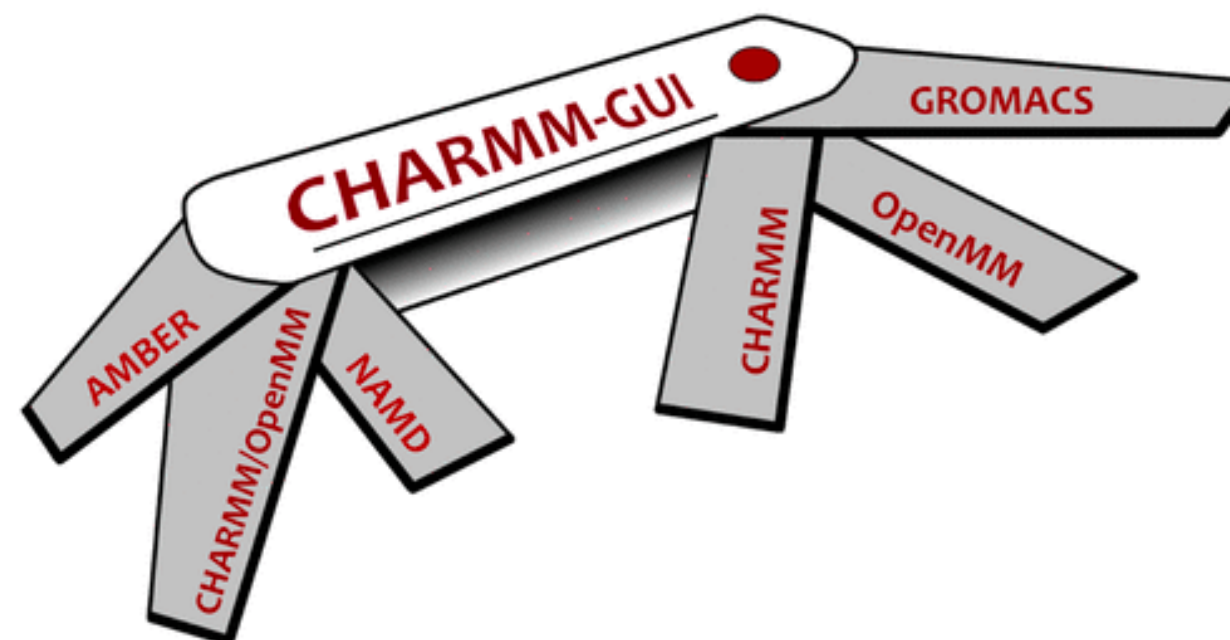
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☐ Explicit grid information for PME FFT

X Y Z
☐ ☐ ☐

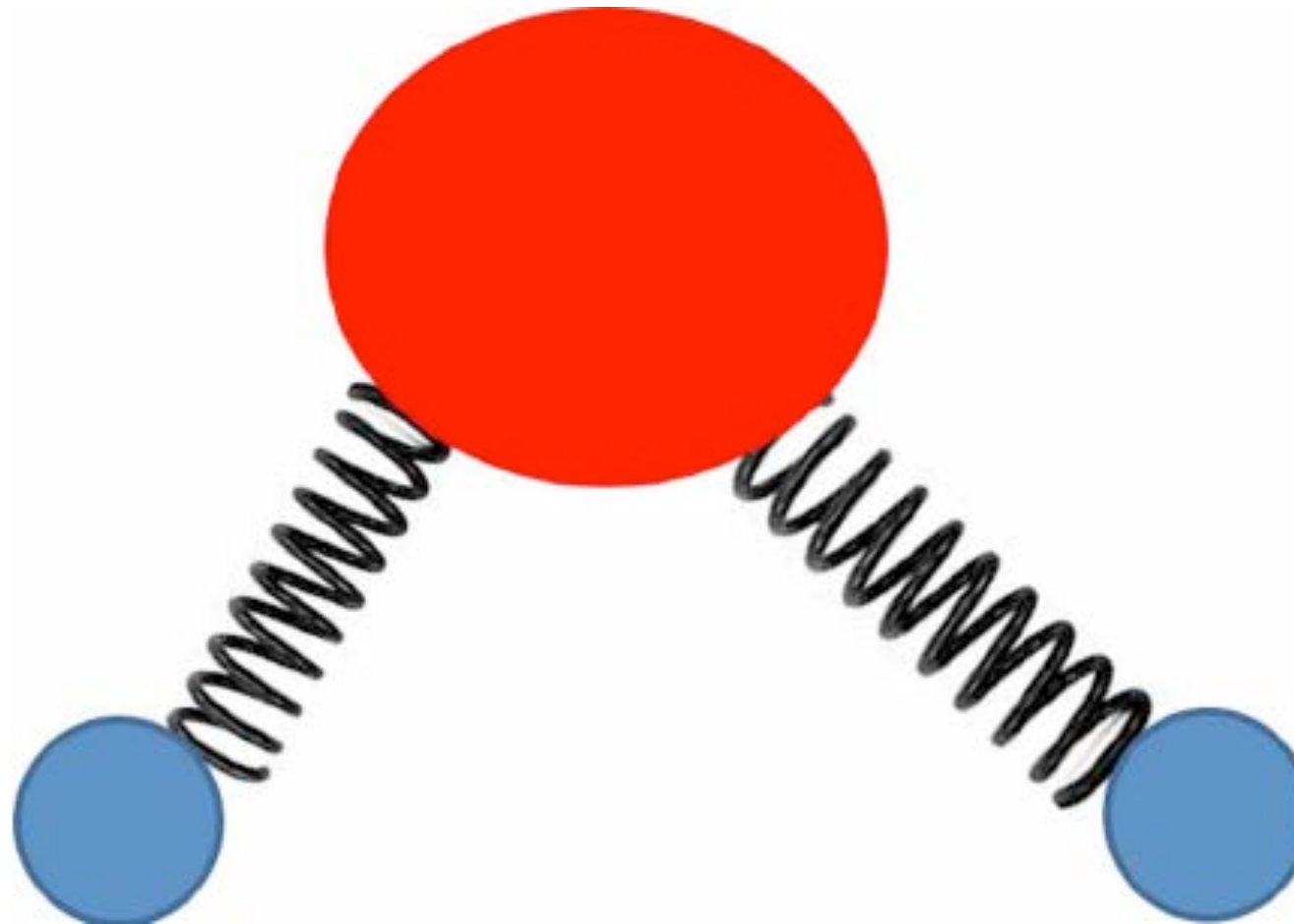
- ☒ NPAT ensemble
☐ NPgT ensemble

Surface Tension 10 (dyne/cm)

Temperature: 303.15 K

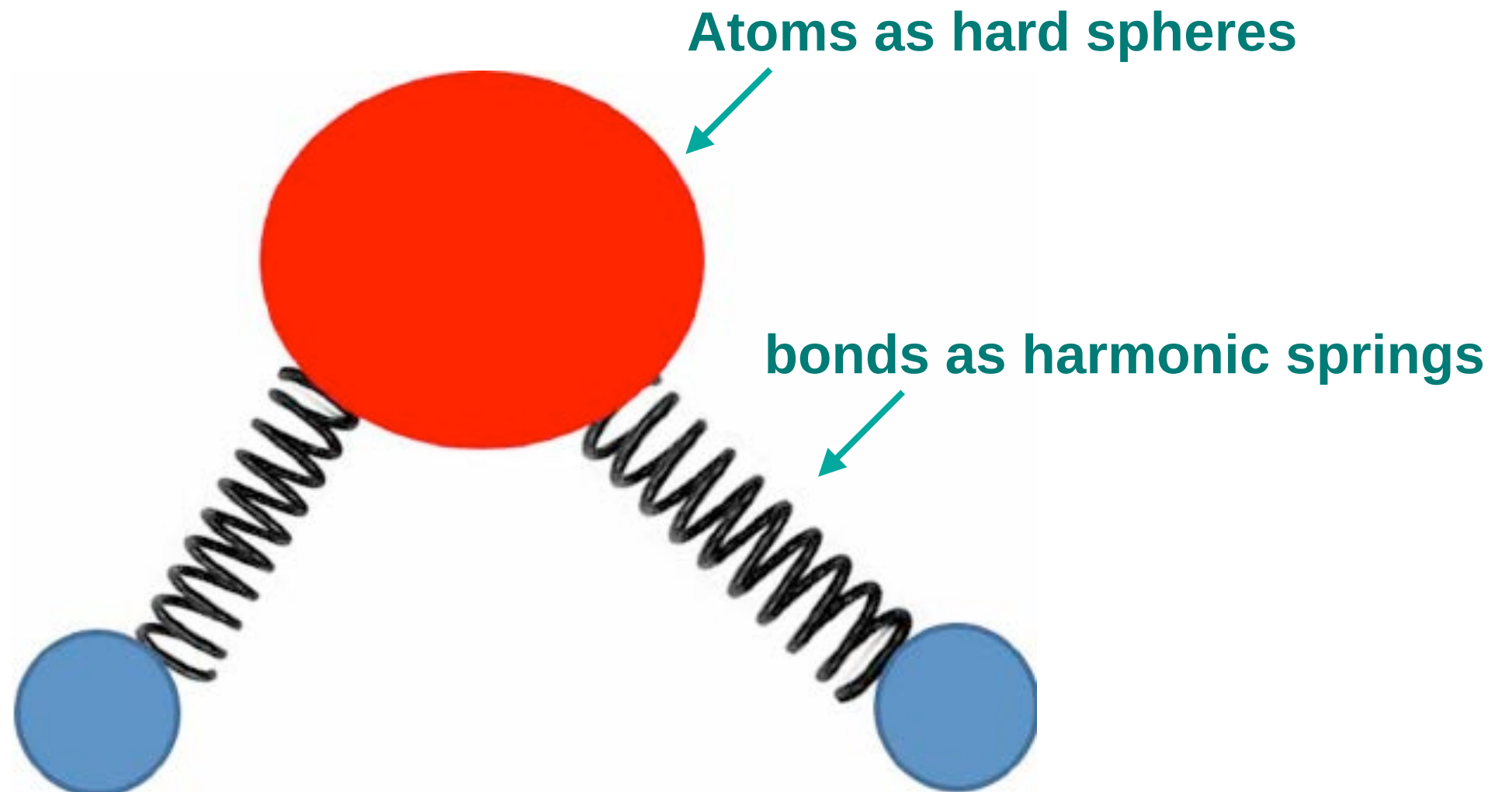


MD simulations is based on classical mechanic



Priya et al, Biomedical Image Analysis and Mining
Techniques for Improved Health Outcomes, 2016

MD simulations is based on classical mechanics



Priya et al, Biomedical Image Analysis and Mining
Techniques for Improved Health Outcomes, 2016

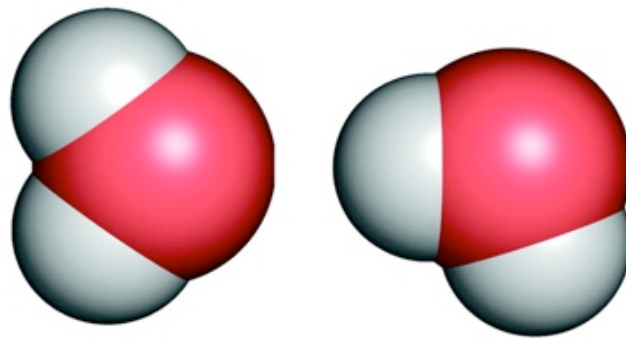
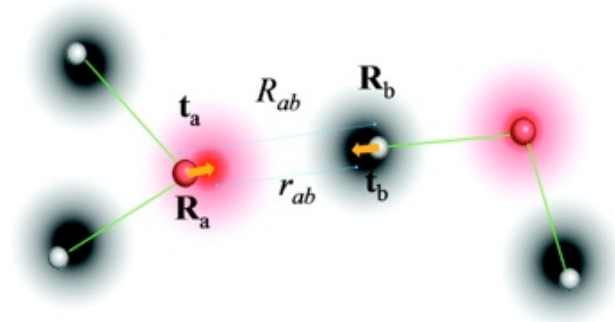
MD simulations: different levels of description

MD simulations: different levels of description

Quantum mechanics

$$\frac{-\hbar^2}{2m}\nabla^2\Psi(r) + V(r)\Psi(r) = E\Psi(r)$$

$$\text{Kinetic Energy} + \text{Potential Energy} = \text{Total Energy}$$



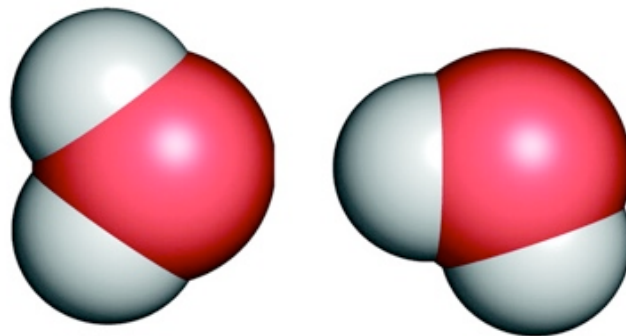
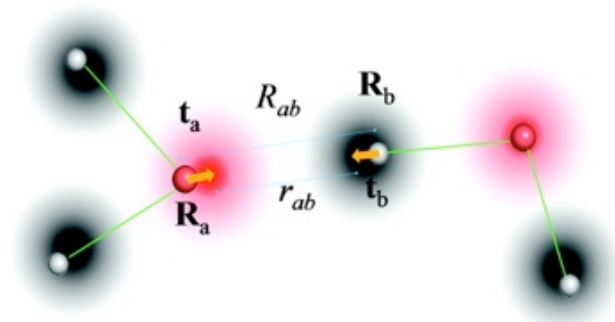
Donchev, PNAS, 2005

MD simulations: different levels of description

Quantum mechanics

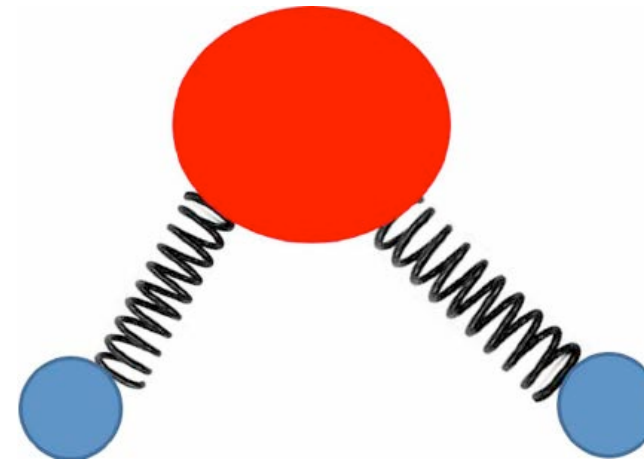
$$\frac{-\hbar^2}{2m}\nabla^2\Psi(r) + V(r)\Psi(r) = E\Psi(r)$$

$$\text{Kinetic Energy} + \text{Potential Energy} = \text{Total Energy}$$



Donchev, PNAS, 2005

Priya et al, Biomedical Image Analysis and Mining
Techniques for Improved Health Outcomes, 2016



Classical potential energy function:

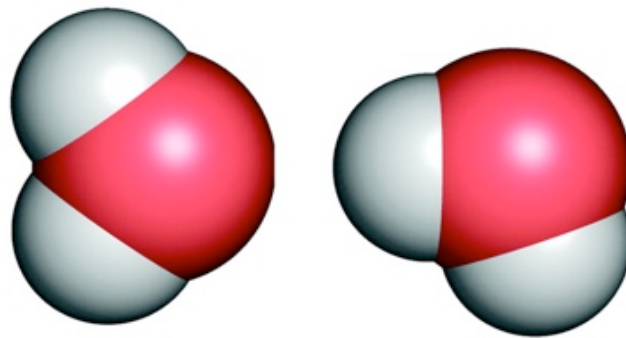
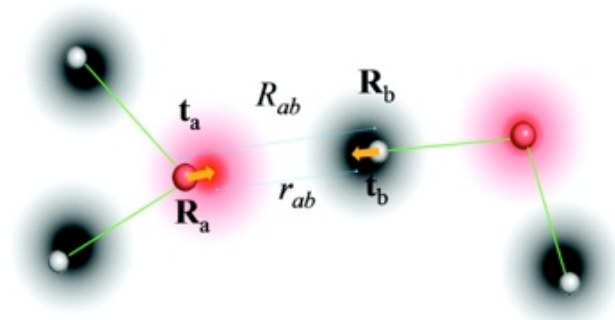
Molecular mechanics (MM)

MD simulations: different levels of description

Quantum mechanics

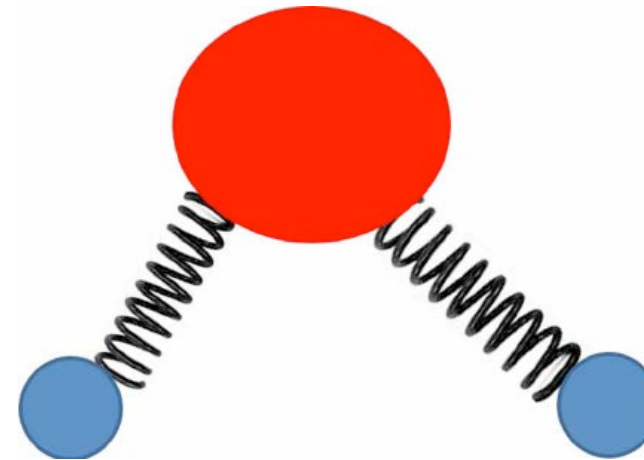
$$\frac{-\hbar^2}{2m}\nabla^2\Psi(r) + V(r)\Psi(r) = E\Psi(r)$$

Kinetic Energy + *Potential Energy* = *Total Energy*



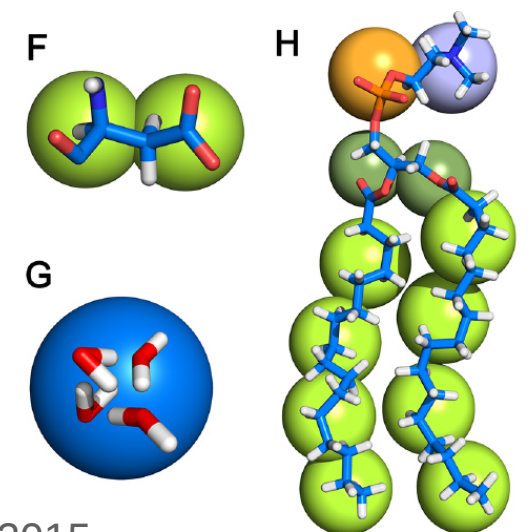
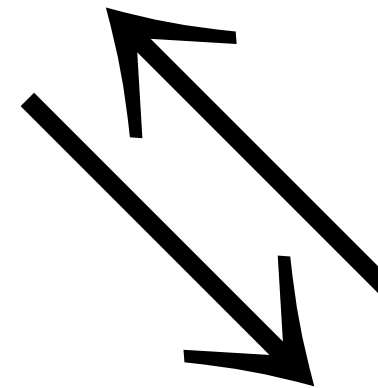
Donchev, PNAS, 2005

Priya et al, Biomedical Image Analysis and Mining Techniques for Improved Health Outcomes, 2016



Classical potential energy function:

Molecular mechanics (MM)



Pluhackova & Böckmann, J Phys, 2015

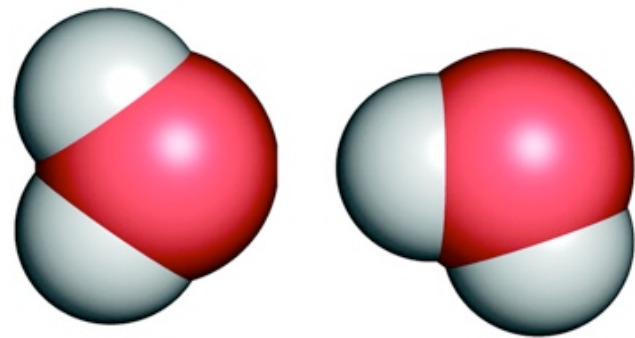
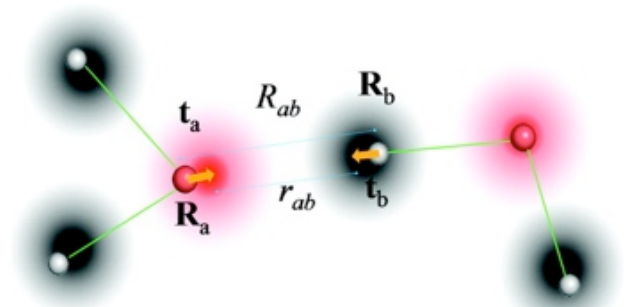
Coarse-grained modelling

MD simulations: different levels of description

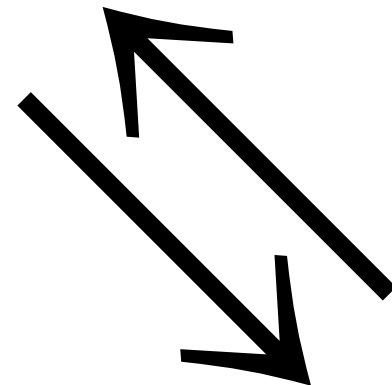
Quantum mechanics

$$\frac{-\hbar^2}{2m}\nabla^2\Psi(r) + V(r)\Psi(r) = E\Psi(r)$$

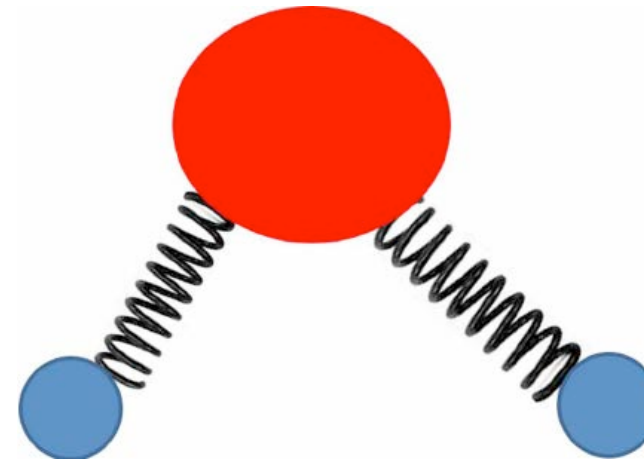
Kinetic Energy + *Potential Energy* = *Total Energy*



Donchev, PNAS, 2005

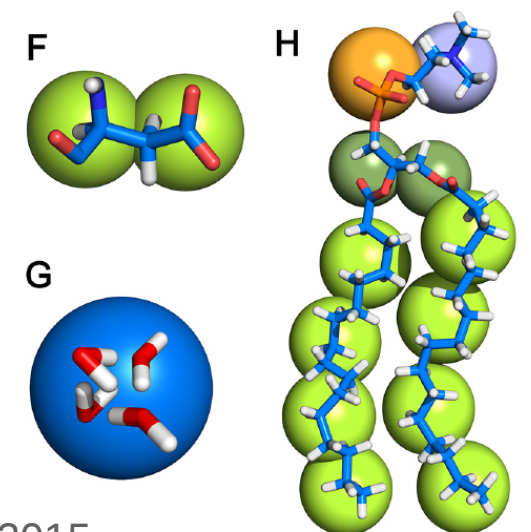
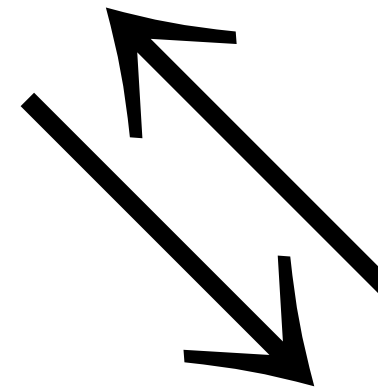


Priya et al, Biomedical Image Analysis and Mining Techniques for Improved Health Outcomes, 2016



Classical potential energy function:

Molecular mechanic (MM)



Pluhackova & Böckmann, J Phys, 2015

Coarse-grained modelling

Combining is possible (multi-scaling)

Like QM and classical (QM/MM)

Applications in molecular membrane biology

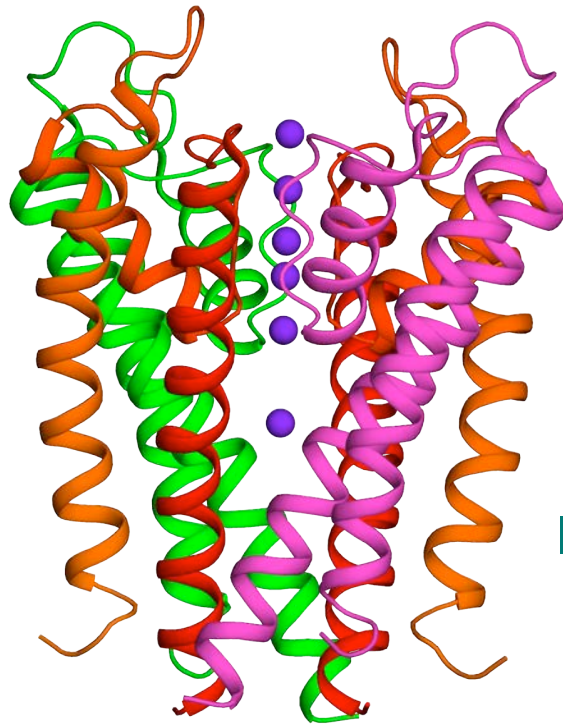
Ion/substrate binding

Protein-lipid interaction

Conformational change

Protein-protein interaction
Post-translational
modifications

Applications in molecular membrane biology



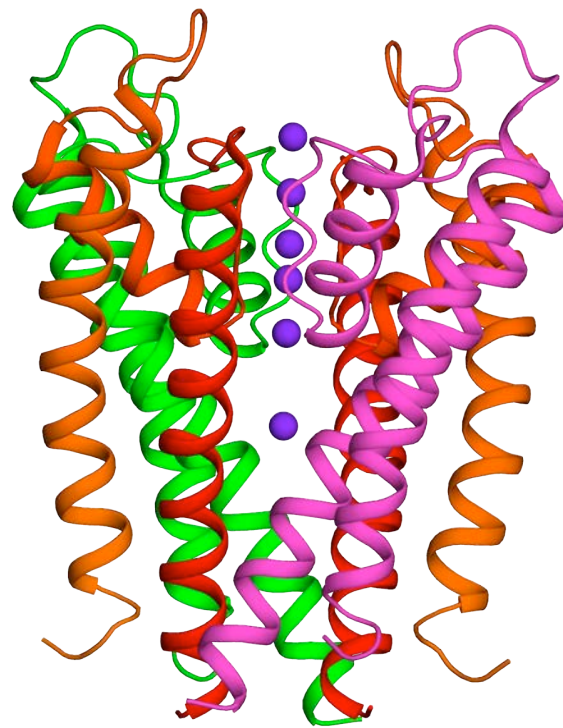
Ion/substrate binding

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Applications in molecular membrane biology

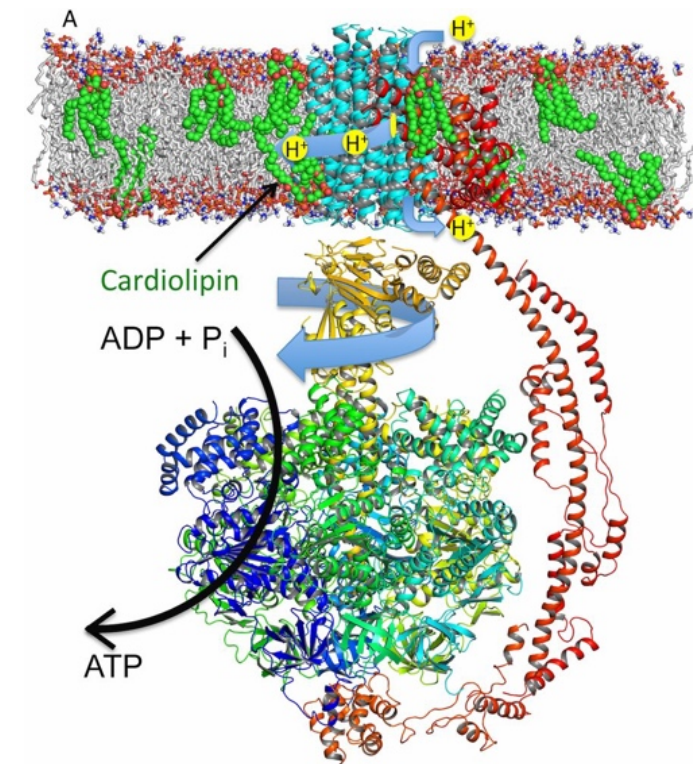


Ion/substrate binding

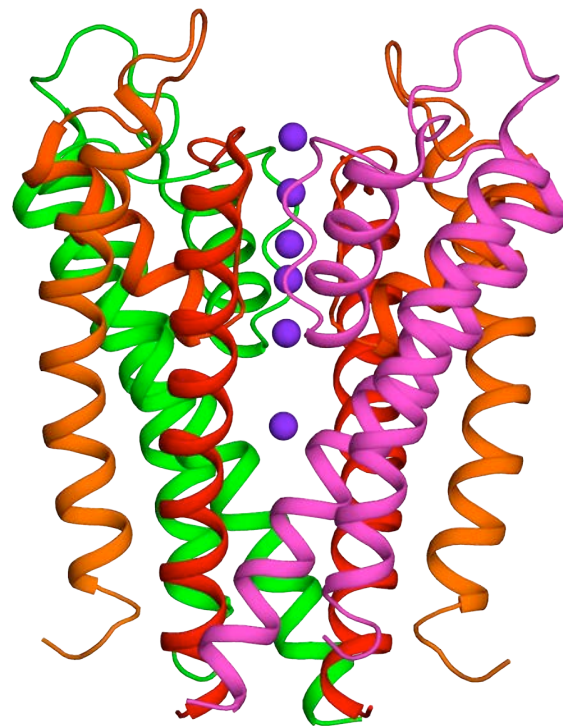
Conformational change

Protein-lipid interaction

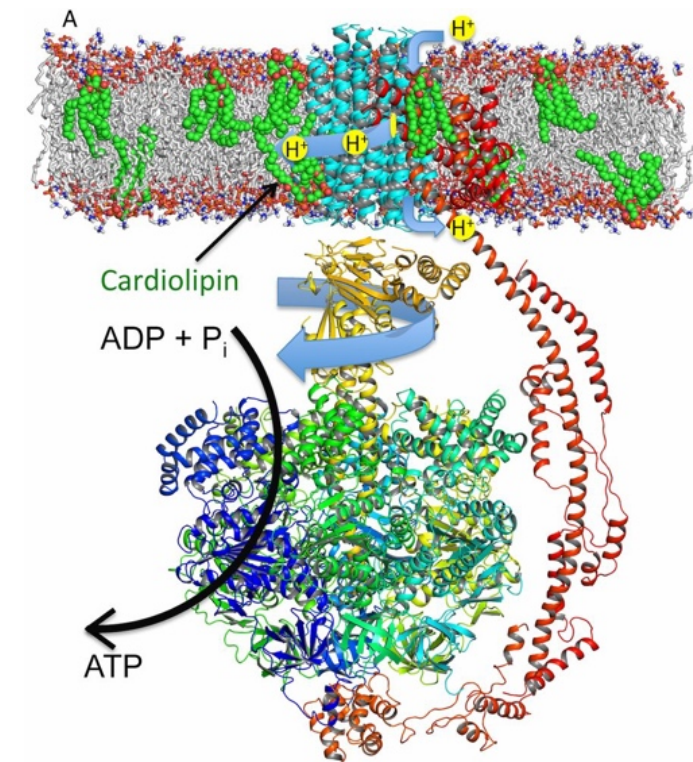
Protein-protein interaction
Post-translational
modifications



Applications in molecular membrane biology



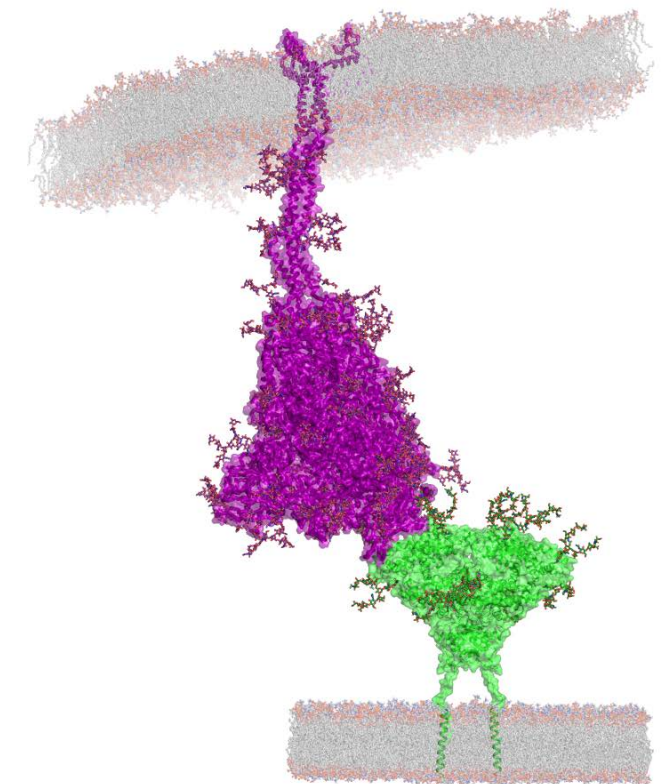
Ion/substrate binding



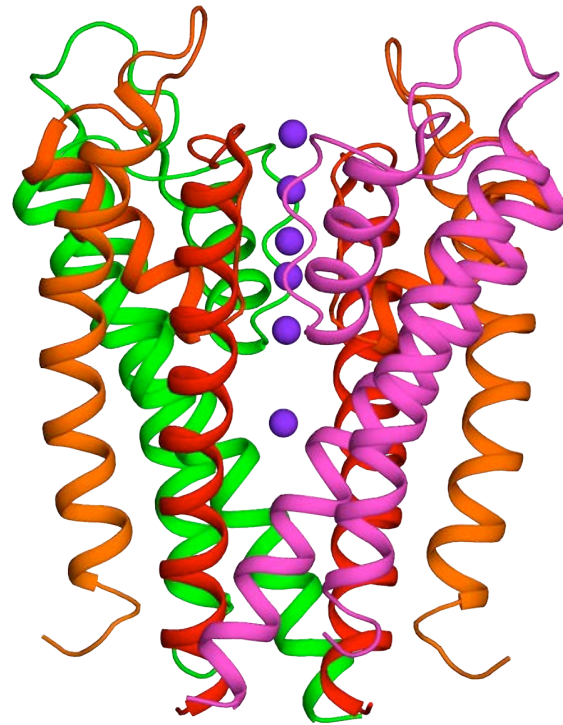
Protein-lipid interaction

Conformational change

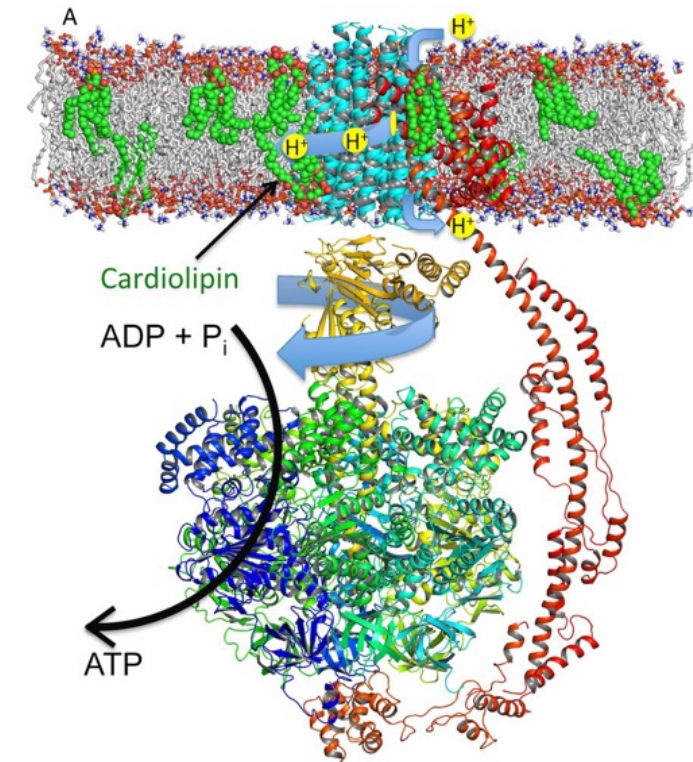
Protein-protein interaction
Post-translational
modifications



Applications in molecular membrane biology

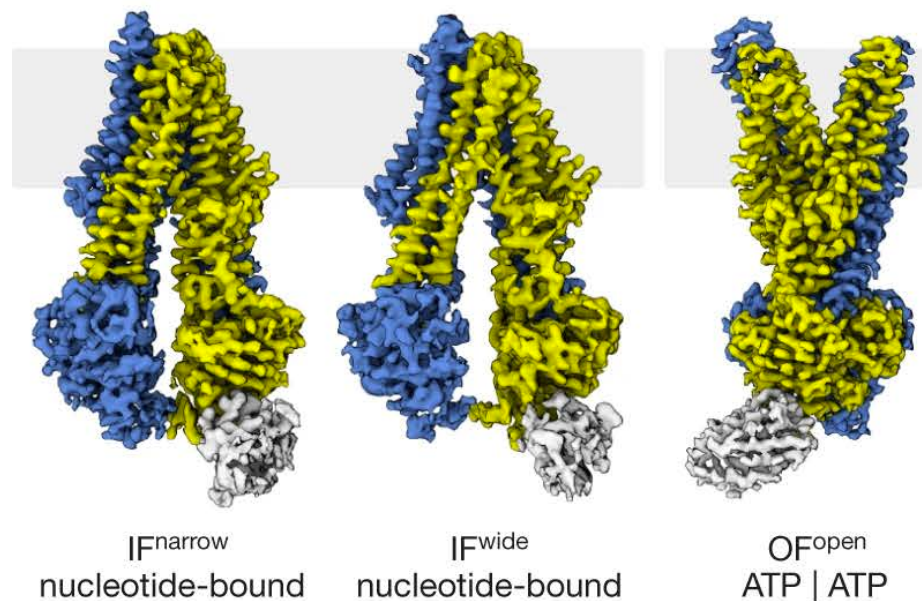


Ion/substrate binding

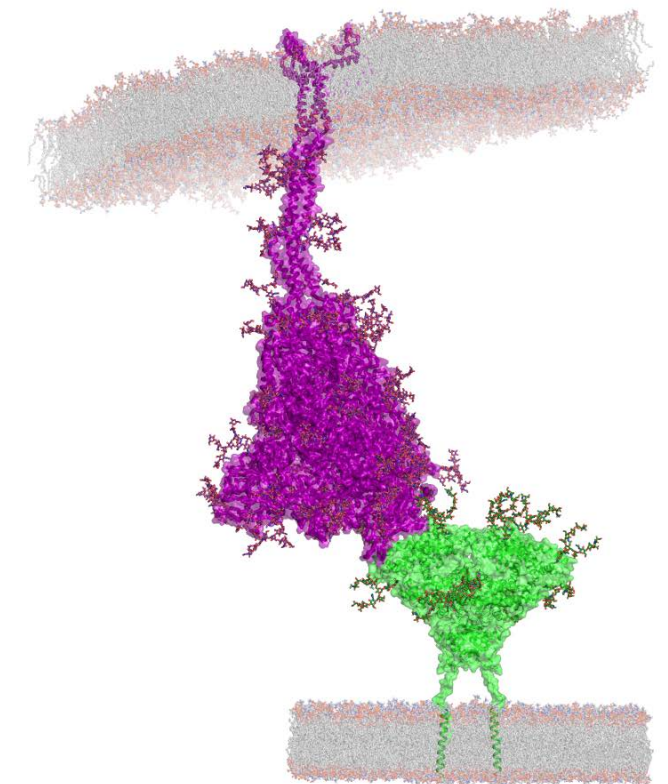


Protein-lipid interaction

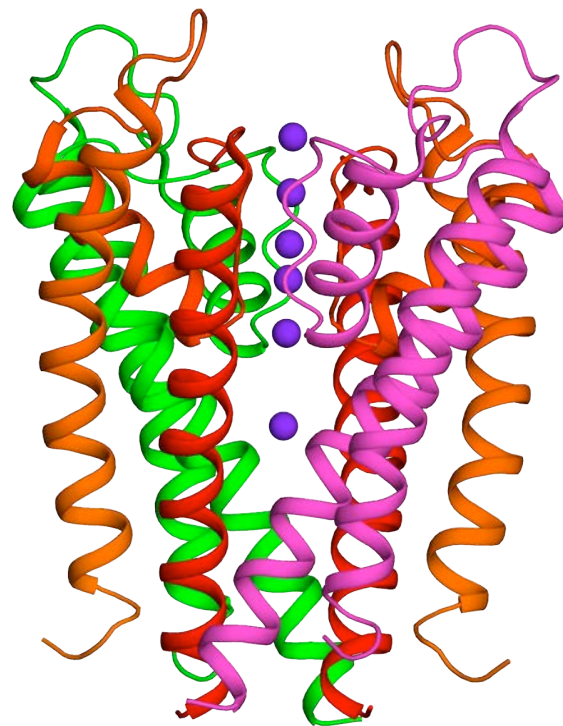
Conformational change



Protein-protein interaction
Post-translational
modifications

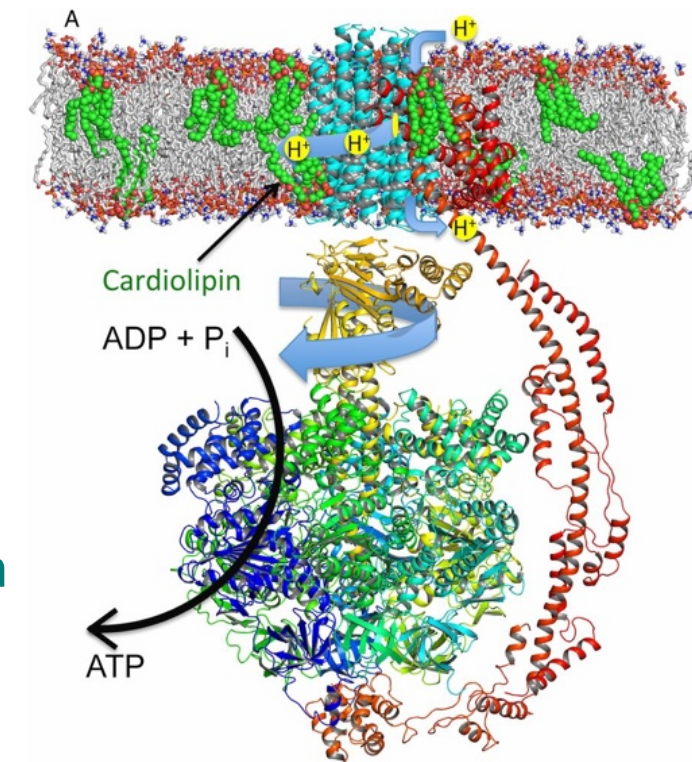


Applications in molecular membrane biology



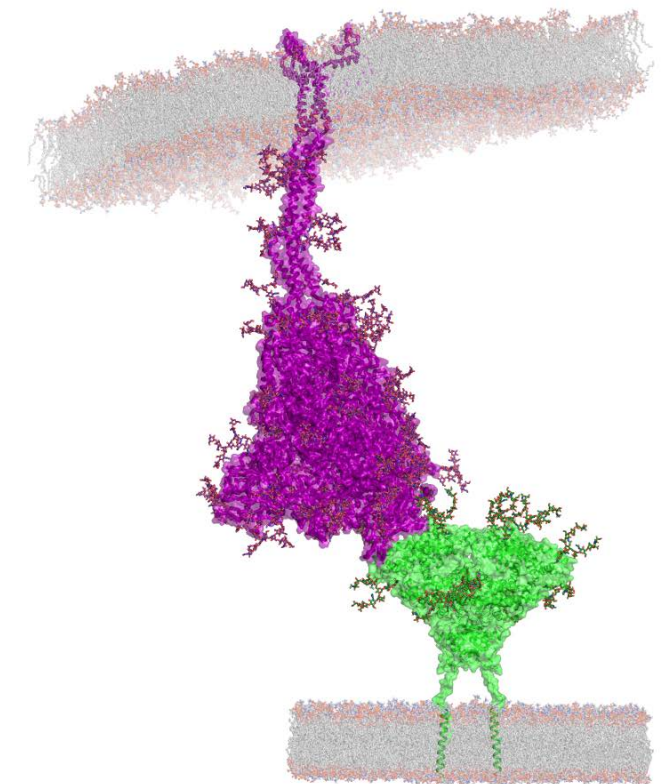
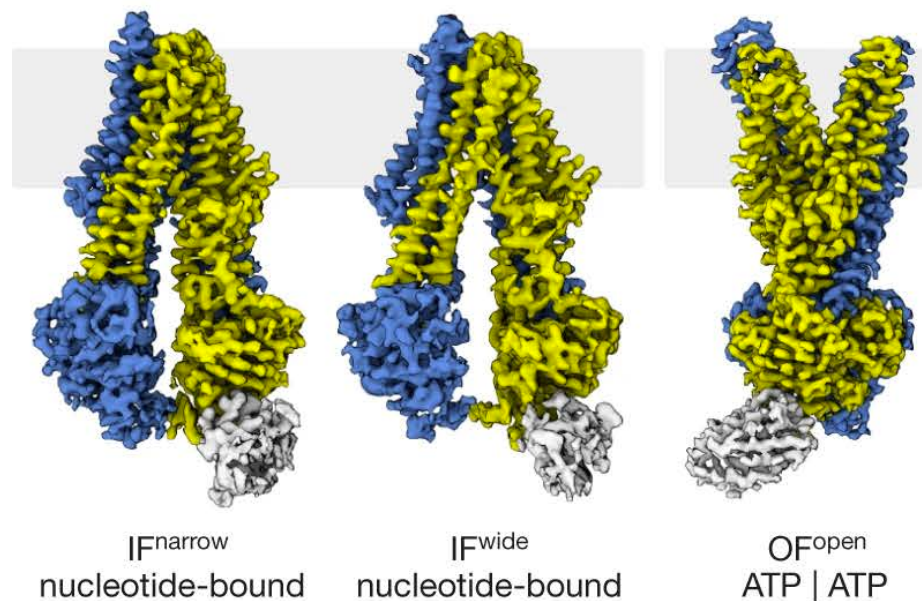
Ion/substrate binding

Protein-lipid interaction

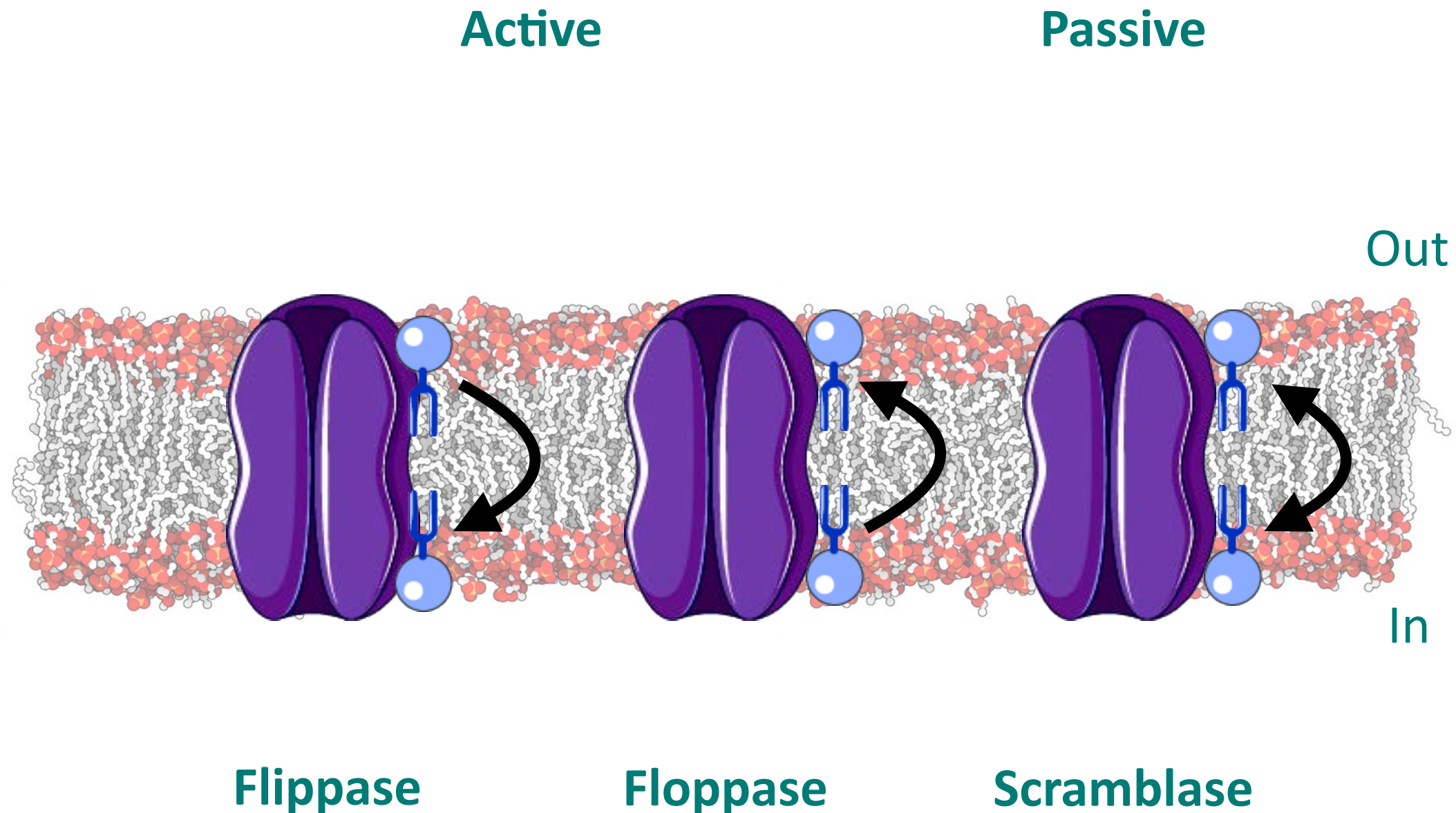


Conformational change

Protein-protein interaction
Post-translational
modifications



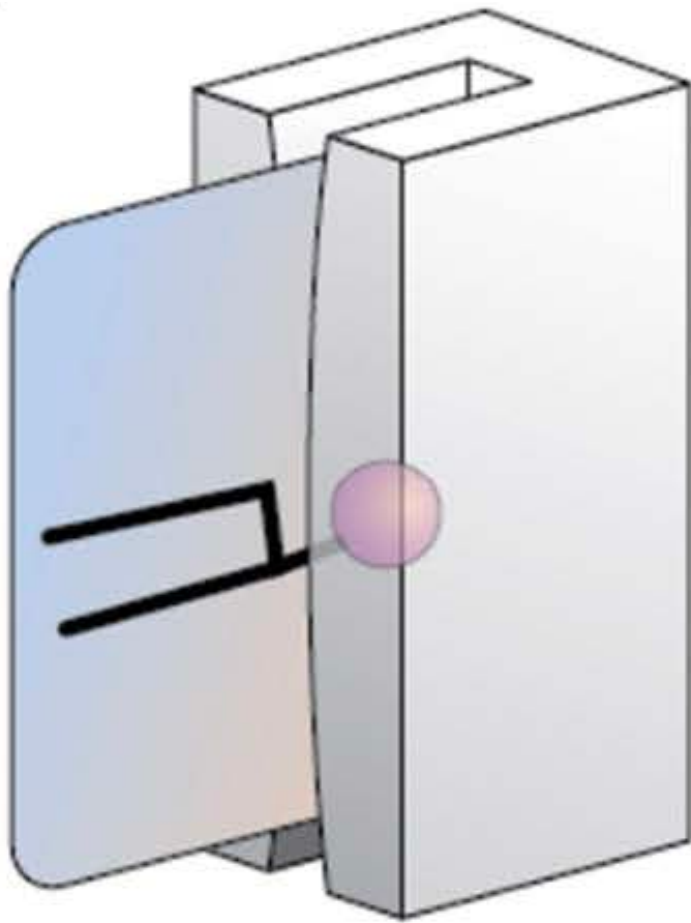
Lipid movement across biological membranes



Mechanisms of Flipping lipids

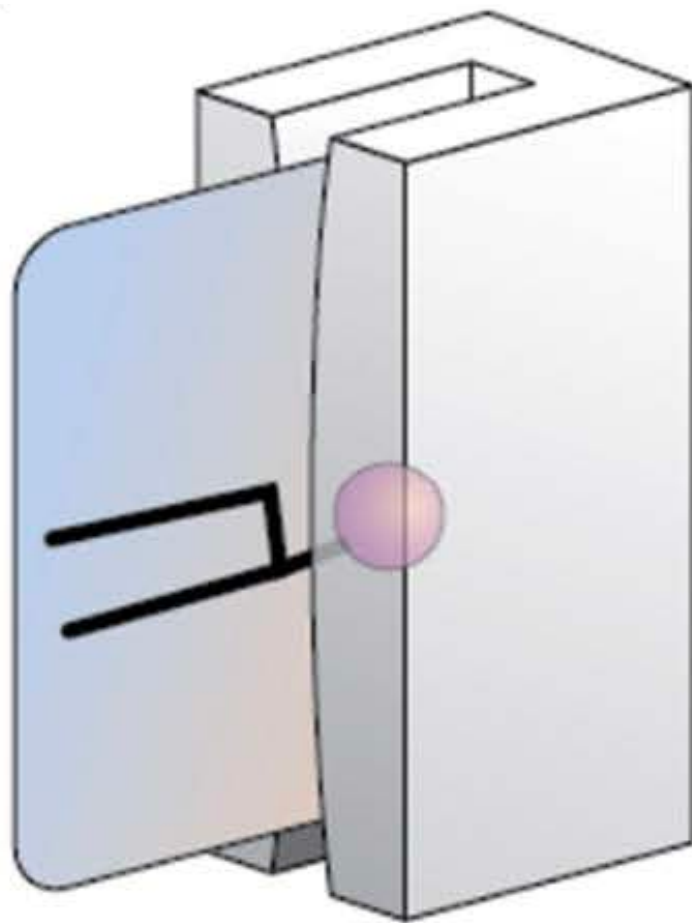
Mechanisms of Flipping lipids

Credit card

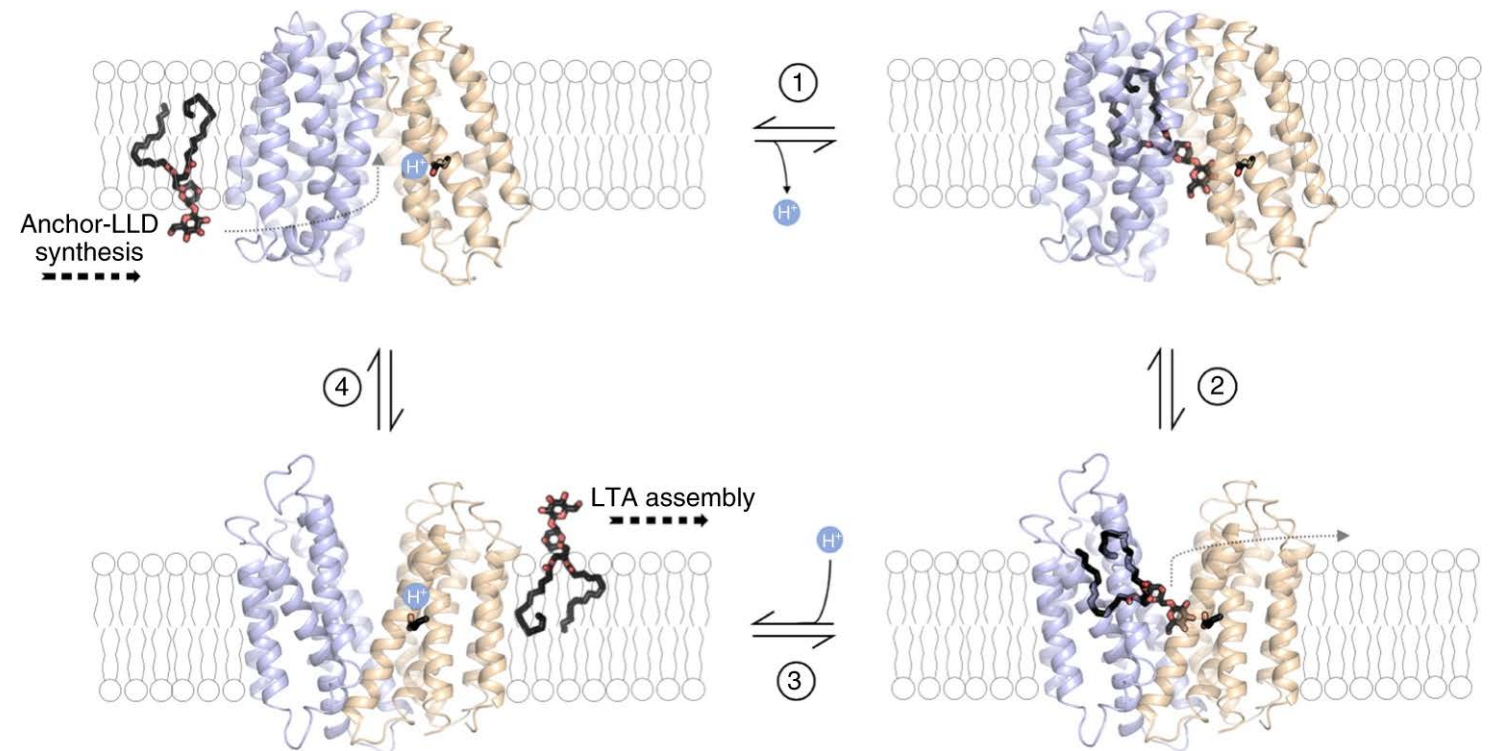


Mechanisms of Flipping lipids

Credit card



Trap-and-flip



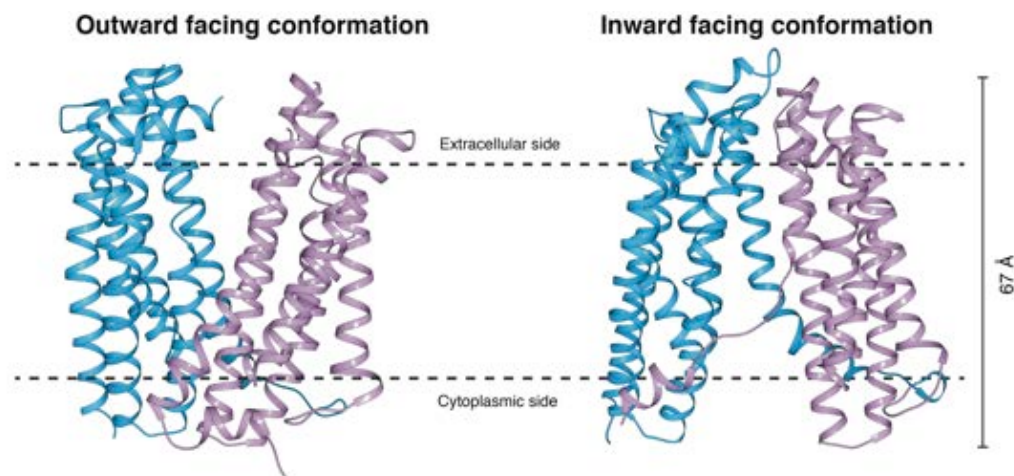


PfMATE



Hartmut Michel

Sandra Zakrzewska



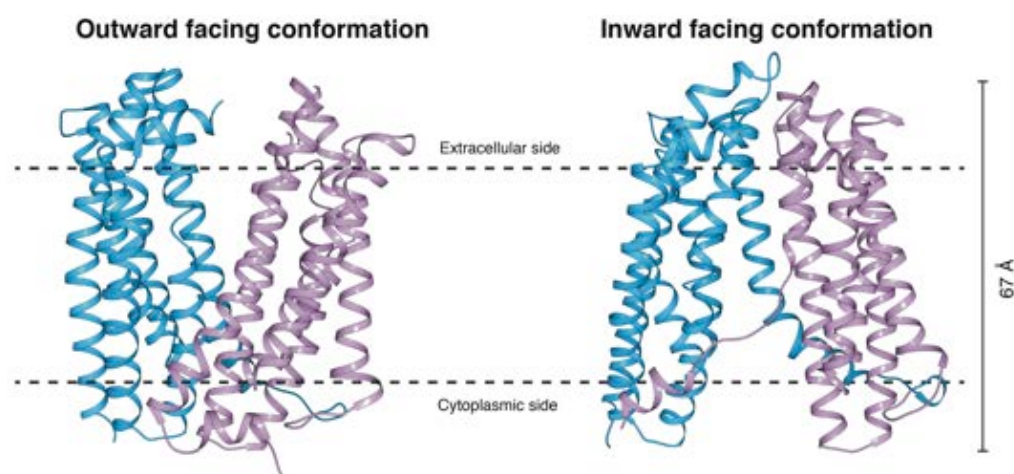


PfMATE

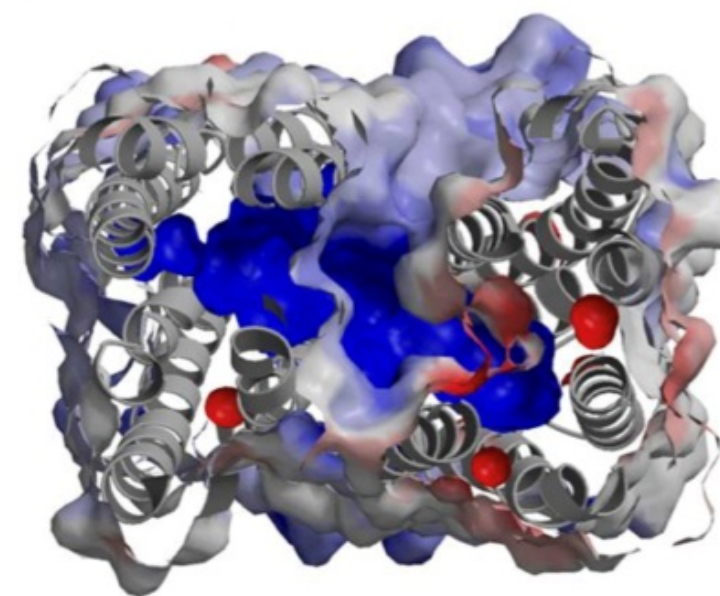


Hartmut Michel

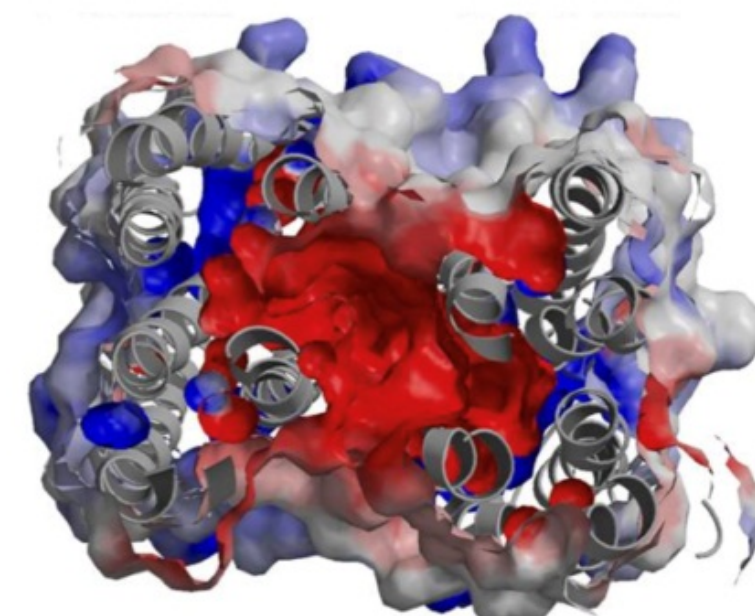
Sandra Zakrzewska



PfMATE (OFC)



NorM_VC



Zakrzewska, Mehdipour, ..., Hummer, Safarian, Michel. PNAS, 2019

Ahmad Reza Mehdipour

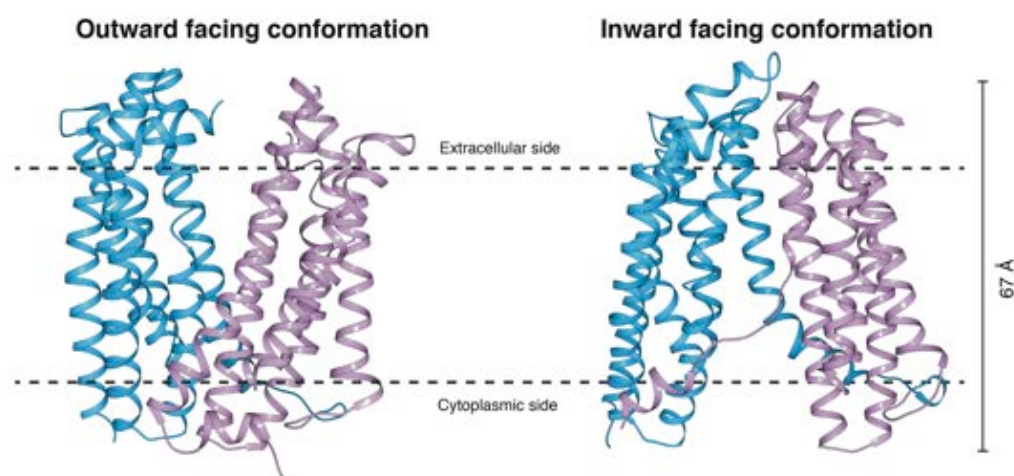


Hartmut Michel

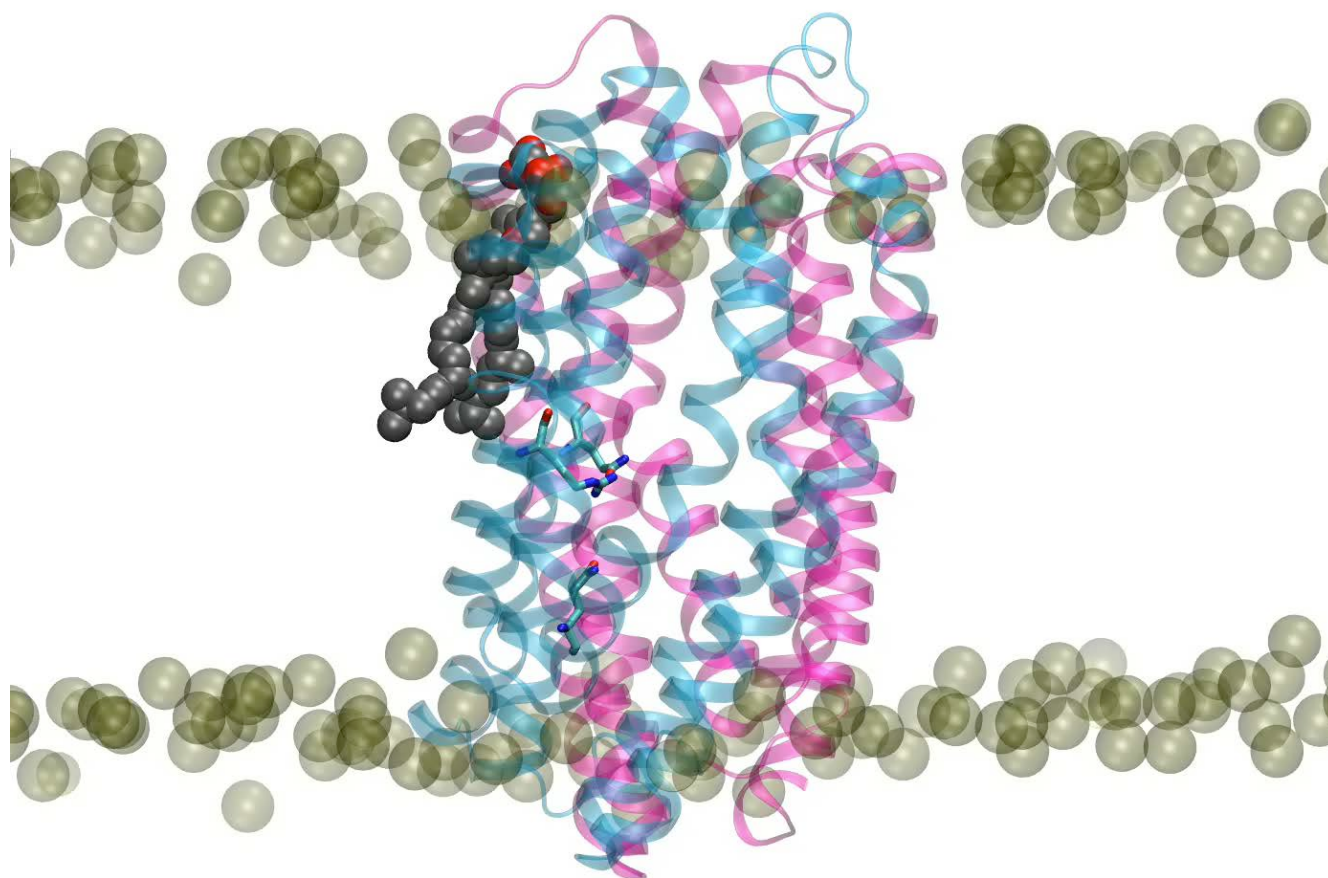
PfMATE



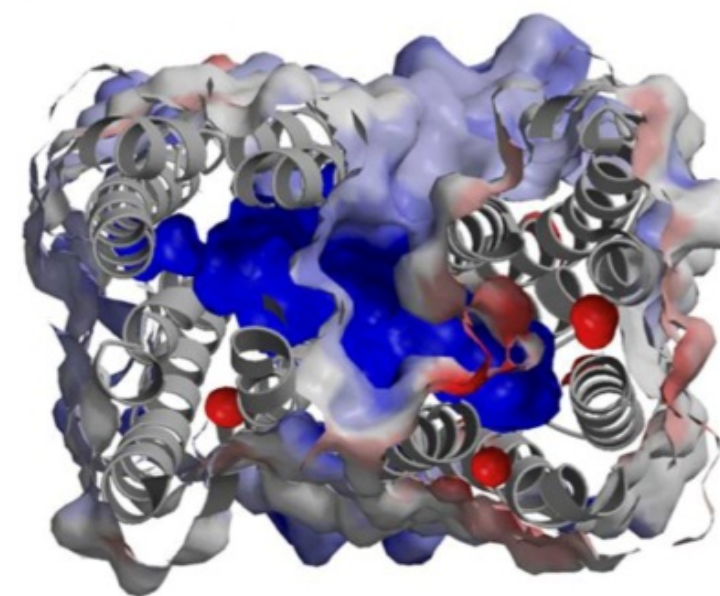
Sandra Zakrzewska



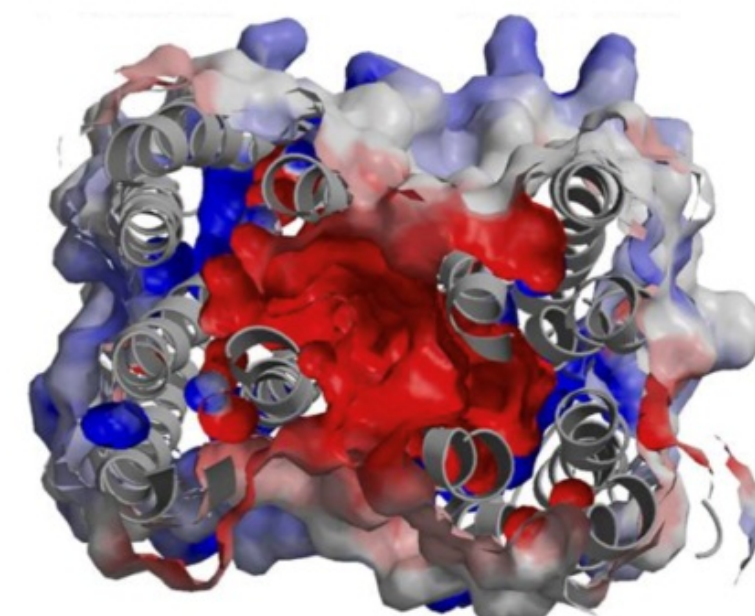
1.5 μ s all-atom simulation of MATE transporter
in an archaeal lipid bilayer



PfMATE (OFC)



NorM_VC



Zakrzewska, Mehdipour, ..., Hummer, Safarian, Michel. PNAS, 2019

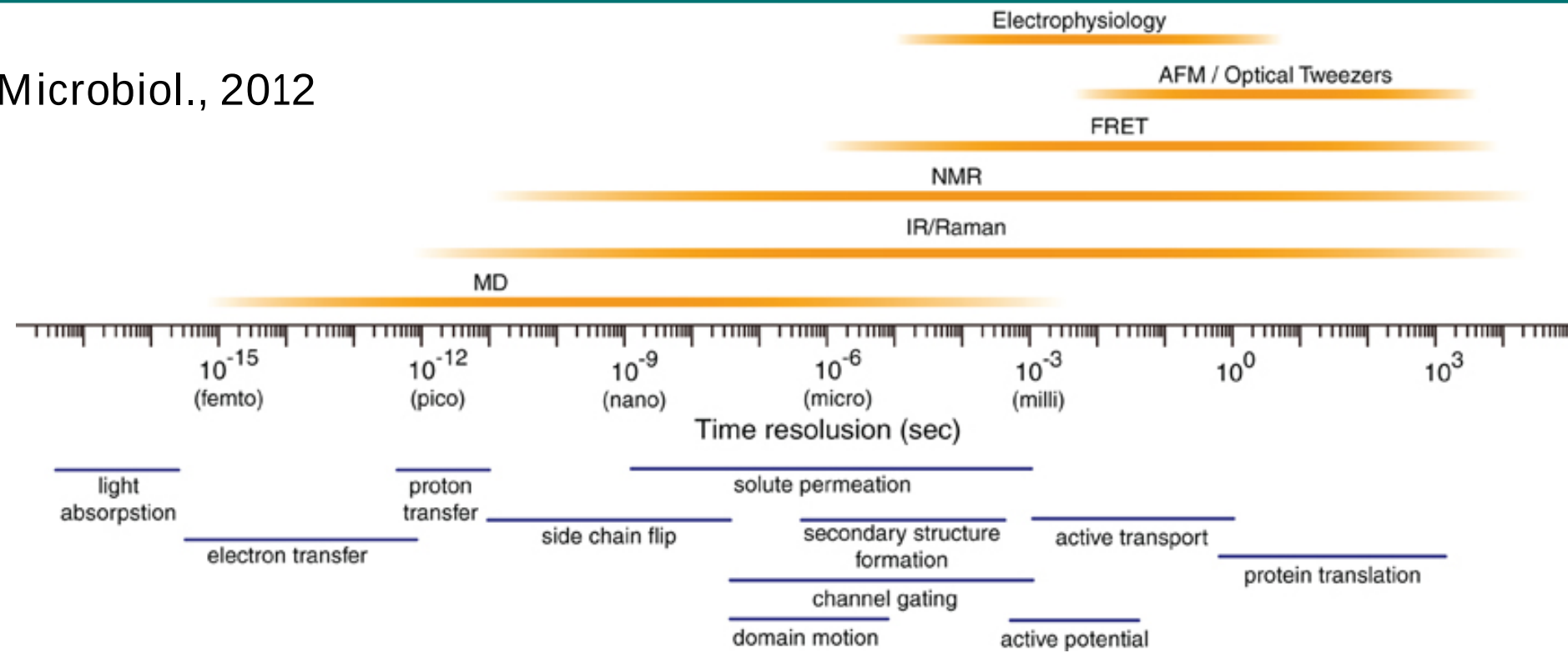
Ahmad Reza Mehdipour

Outline

- Theoretical Biophysics
- Molecular dynamics (MD) simulations
- Applications of MD simulations in membrane biology
 - Protein-lipid interaction: lipid flippase
- **Advanced methods**
- Future directions

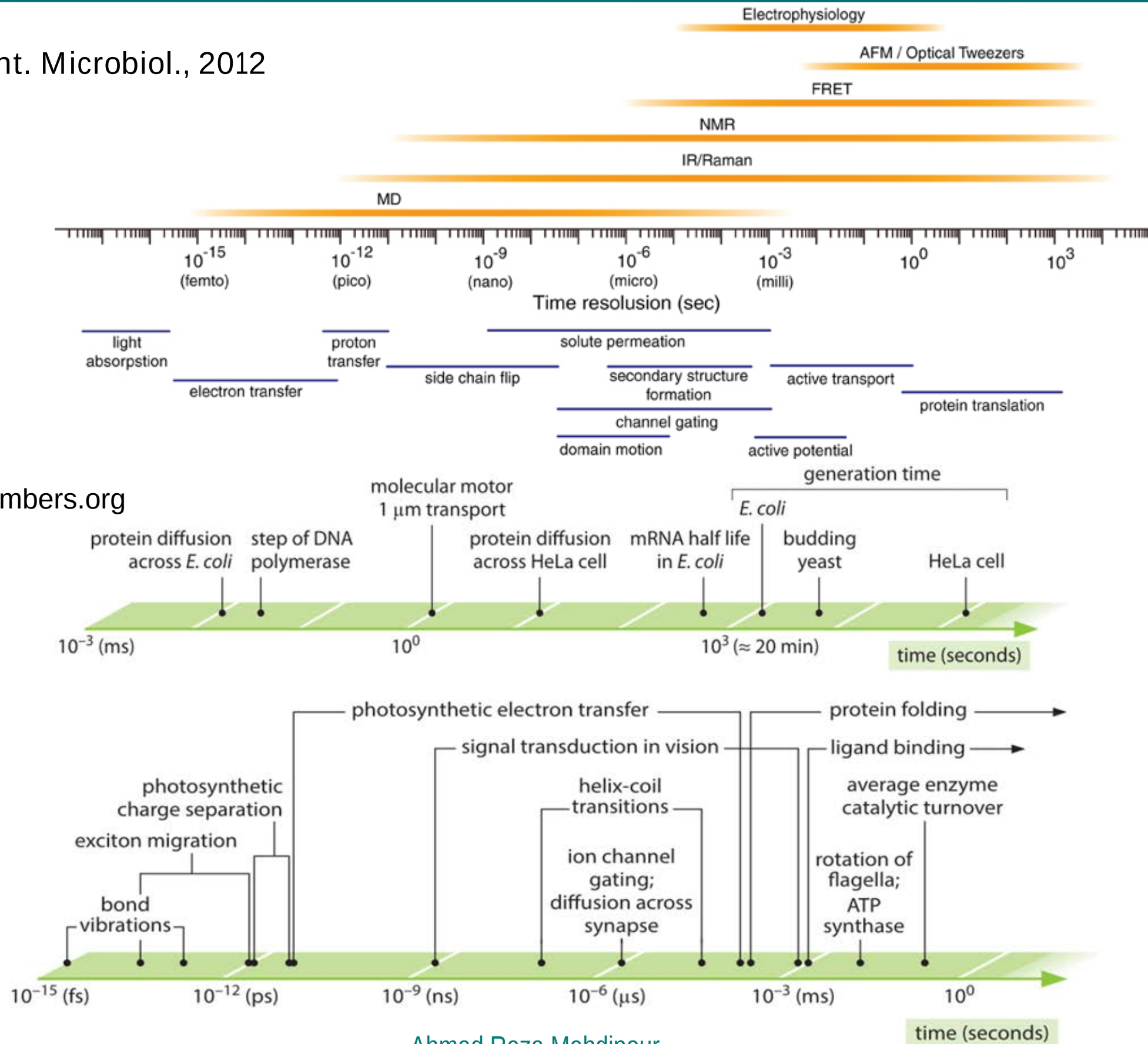
Time scale problem

Ode et al. Front. Microbiol., 2012



Time scale problem

Ode et al. Front. Microbiol., 2012



book.bionumbers.org

Time scale problem: solutions

Time scale problem: solutions

Solutions

Time scale problem: solutions

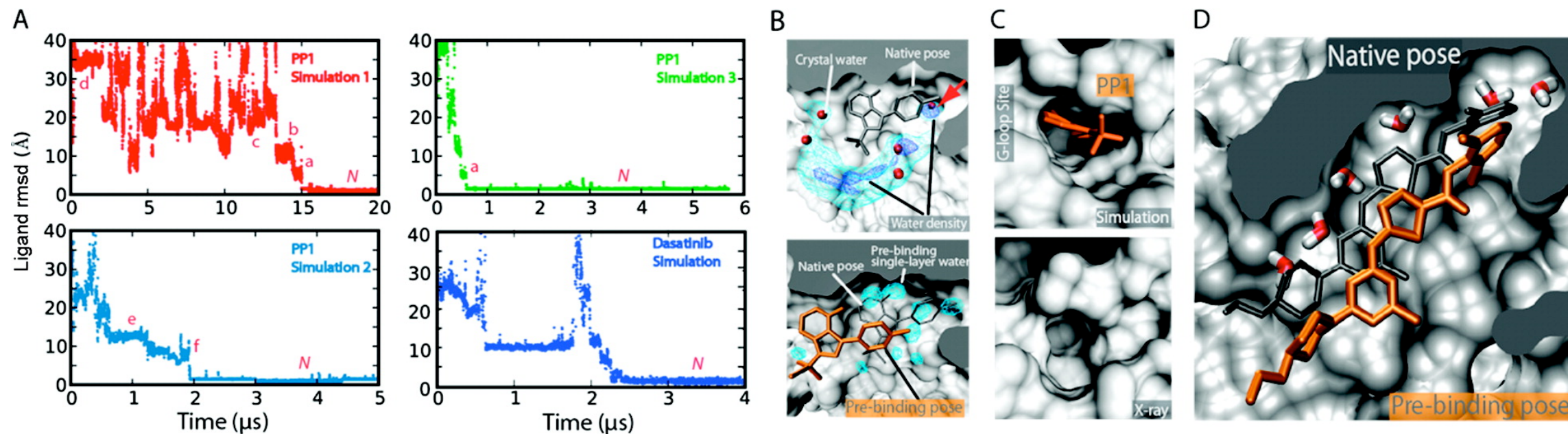
Solutions

- ★ Specialised MD supercomputers: Anton

Time scale problem: solutions

Solutions

★ Specialised MD supercomputers: Anton



Time scale problem: solutions

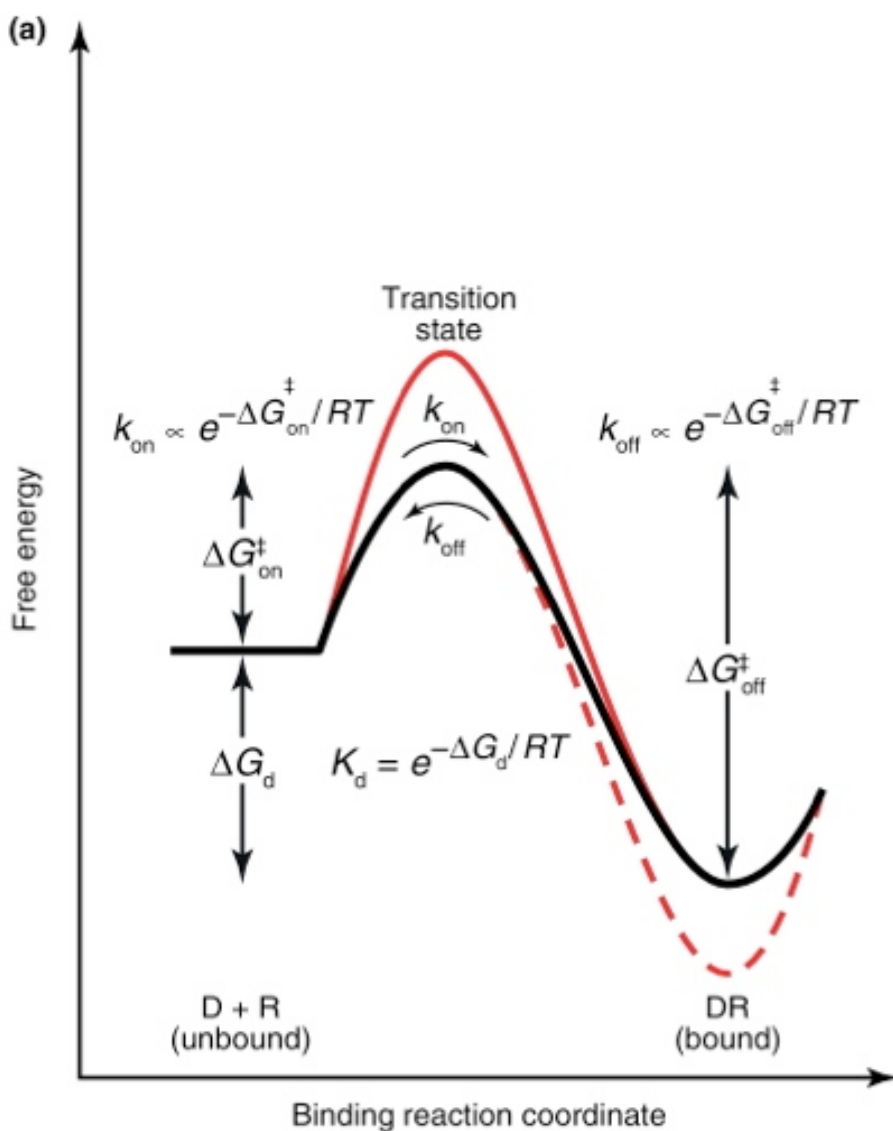
Solutions

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Time scale problem: solutions

Solutions

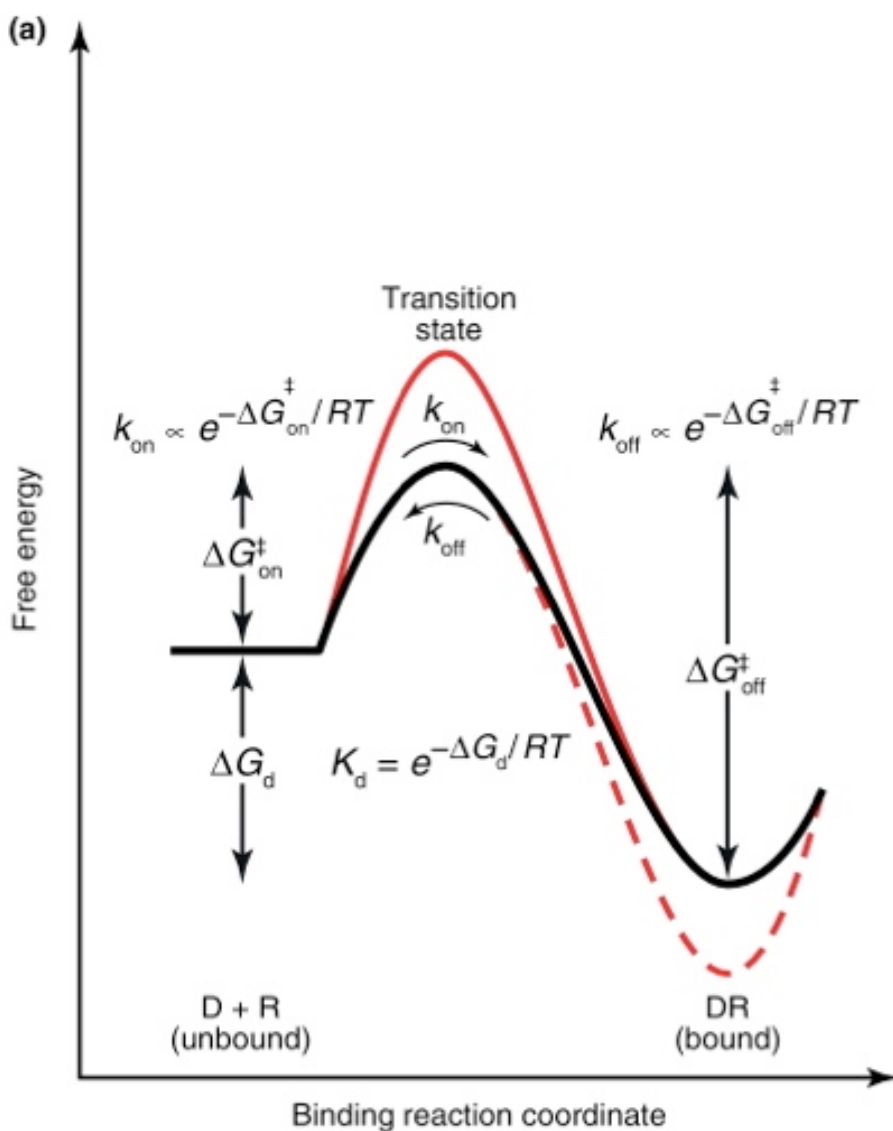
- ★ Specialised MD supercomputers: Anton
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Time scale problem: solutions

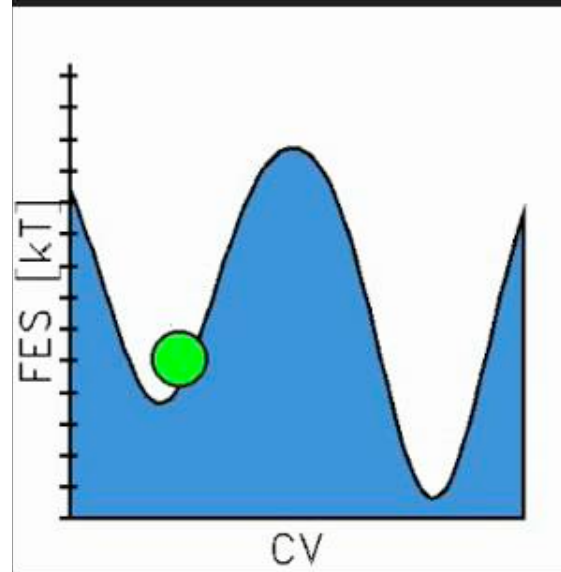
Solutions

- ★ Specialised MD supercomputers: Anton
- ★ Enhanced Sampling

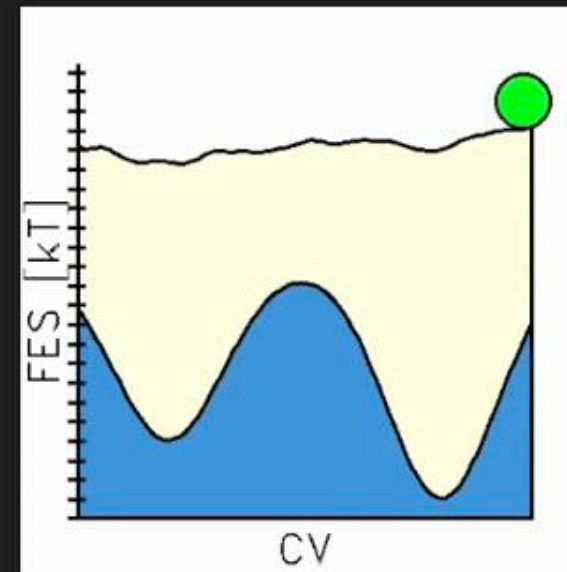


Metadynamics

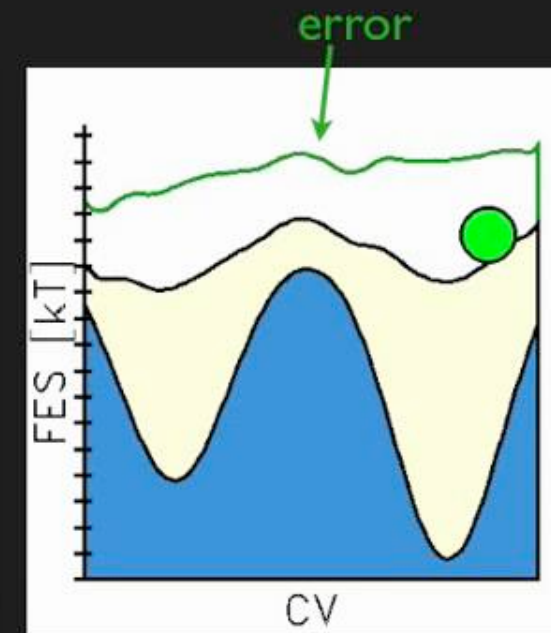
no metadynamics



plain metadynamics



well-tempered metadynamics



Laio and Parrinello,
PNAS (2002)

Barducci, Bussi and
Parrinello
PRL (2008)

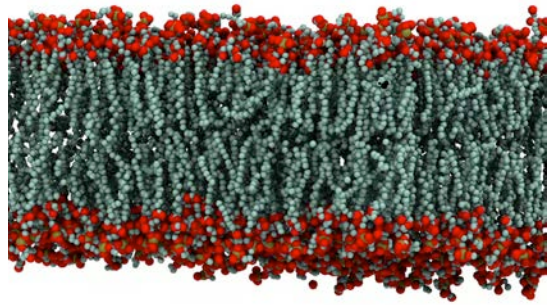
movies by Giovanni Bussi

Outline

- Theoretical Biophysics
- Molecular dynamics (MD) simulations
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- **Future directions**

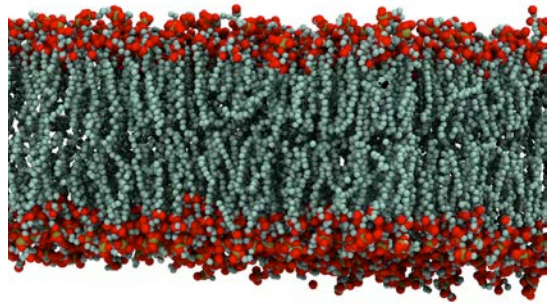
Future: from molecular biology to cell biology

Future: from molecular biology to cell biology

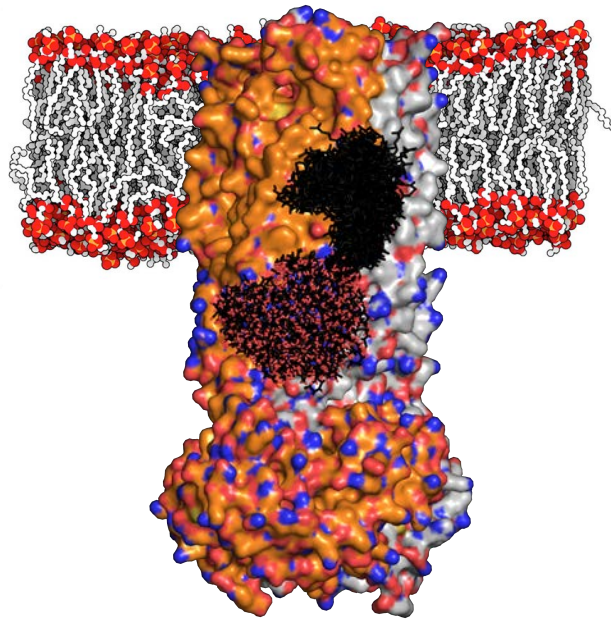


10×10×14 nm
~ 100,000 Atoms

Future: from molecular biology to cell biology

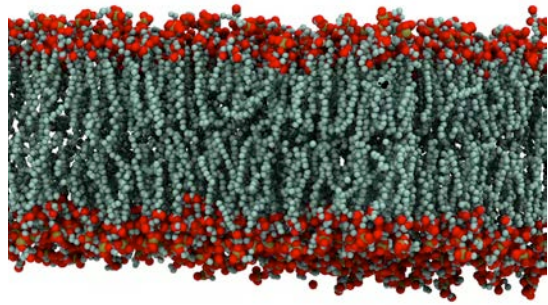


$10 \times 10 \times 14$ nm
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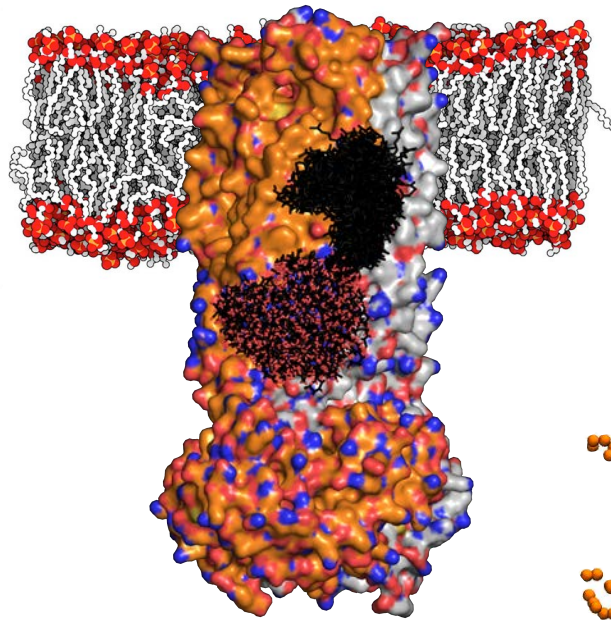


$14 \times 14 \times 16$ nm
~ 280,000 Atoms

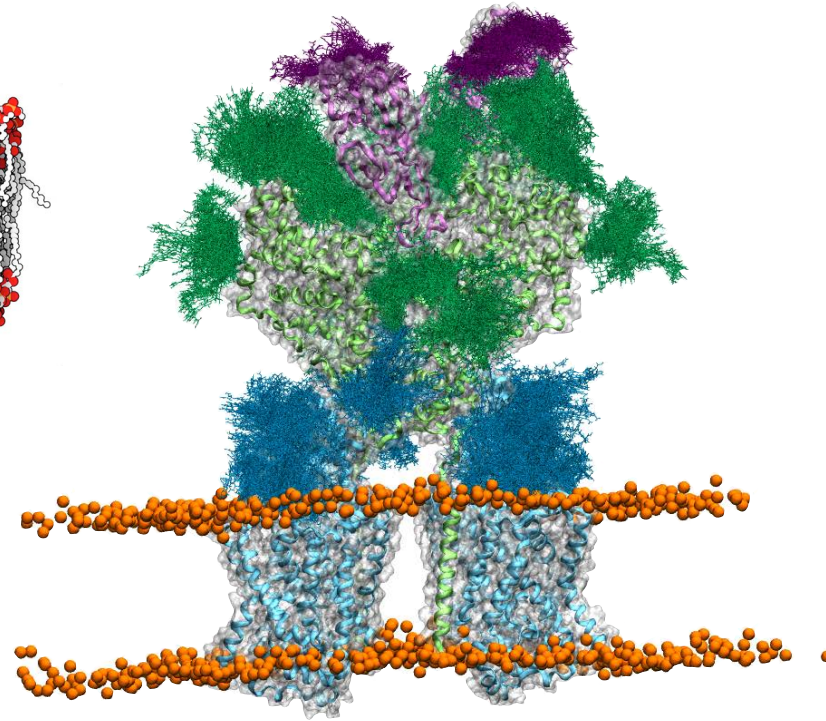
Future: from molecular biology to cell biology



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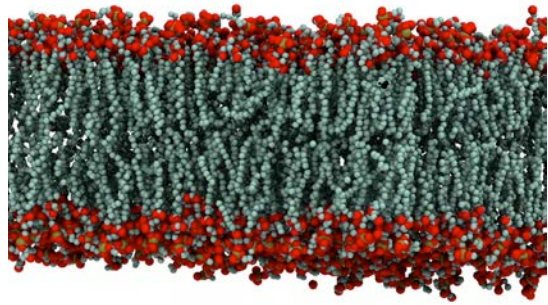


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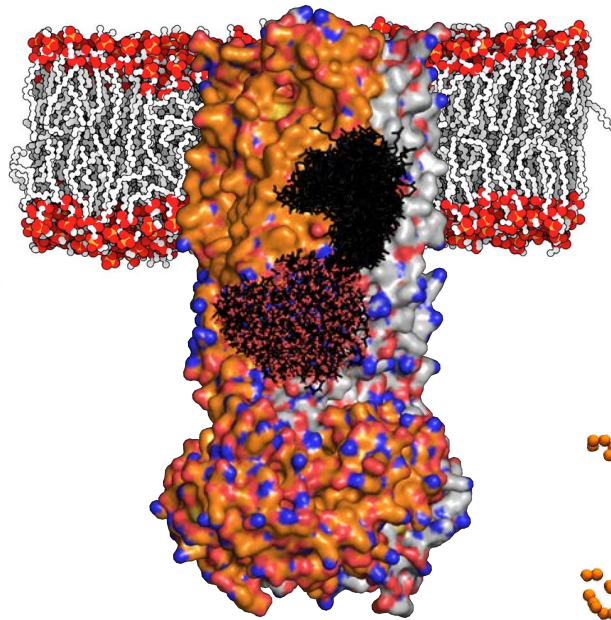


$21 \times 21 \times 26$ nm
~ 1,000,000 Atoms

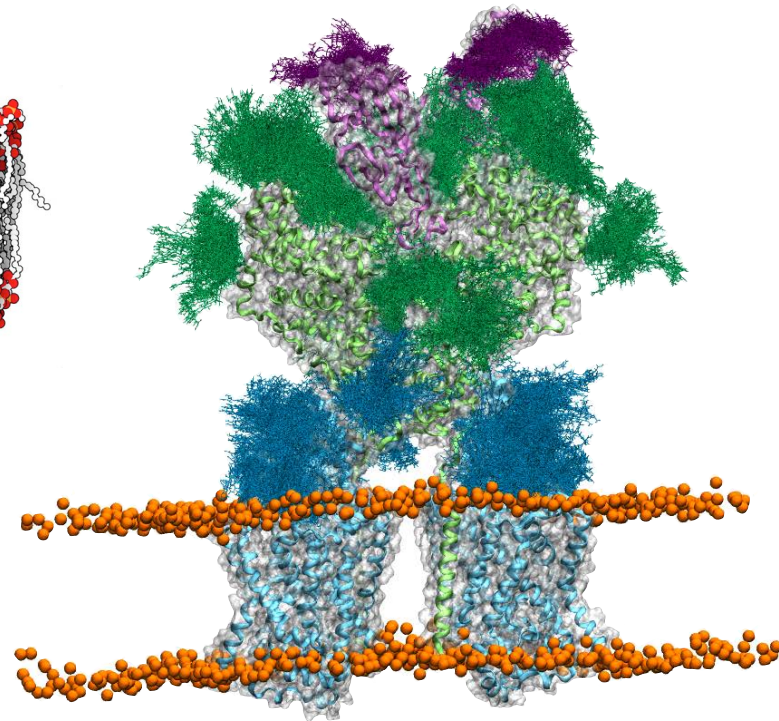
Future: from molecular biology to cell biology



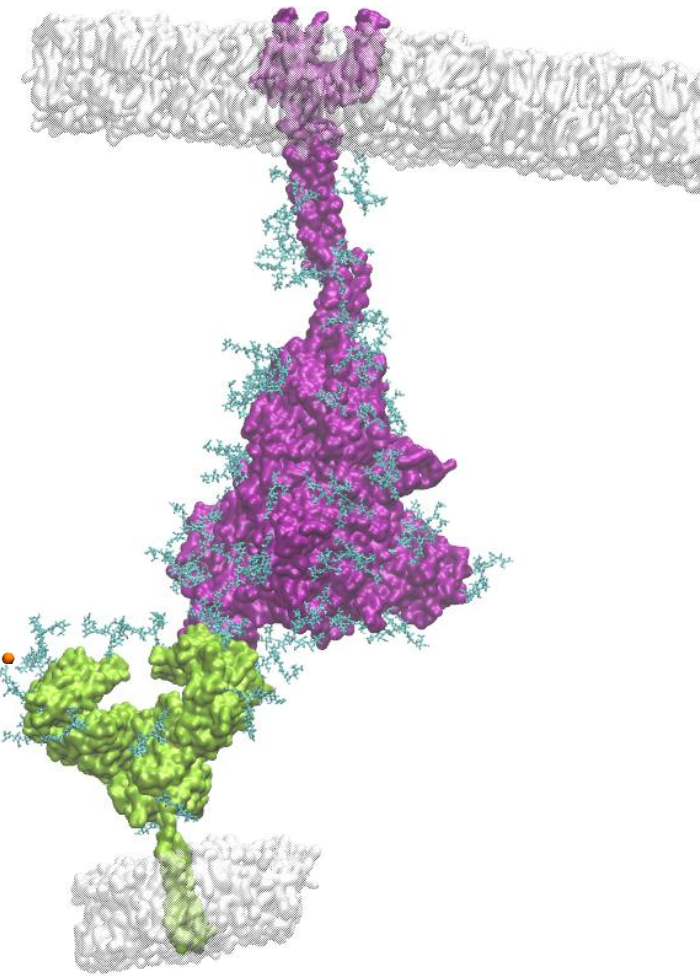
10×10×14 nm
~ 100,000 Atoms



14×14×16 nm
~ 280,000 Atoms

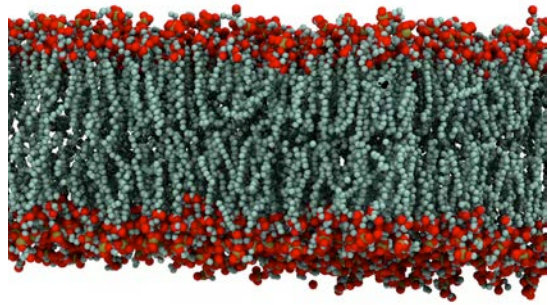


21×21×26 nm
~ 1,000,000 Atoms

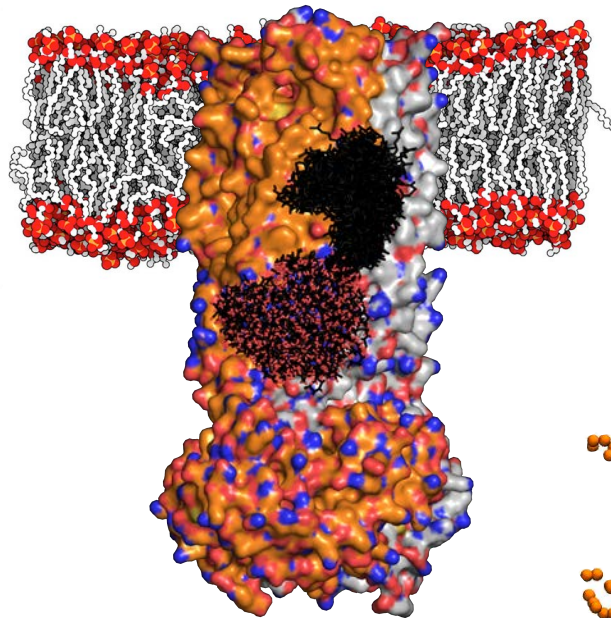


30×30×65 nm
~ 5,000,000 Atoms

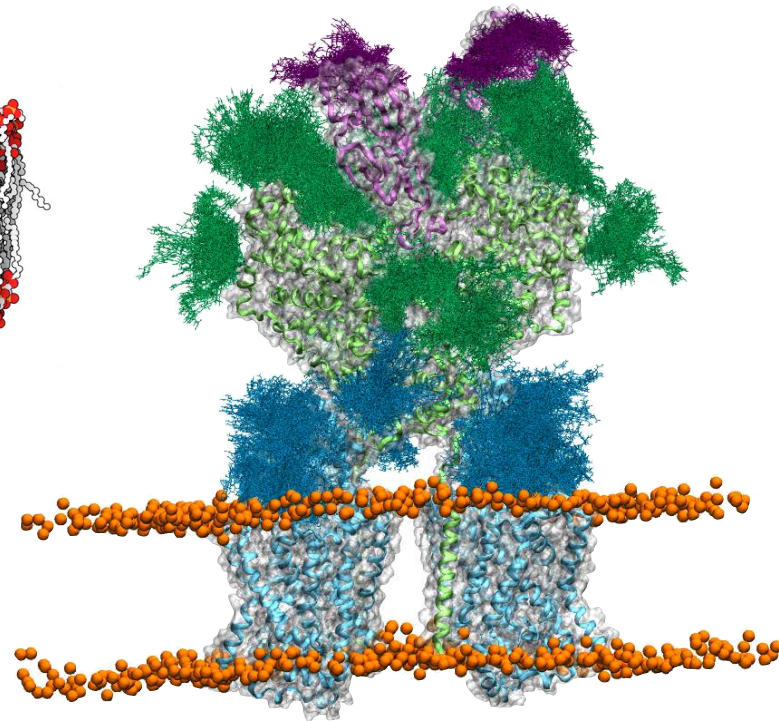
Future: from molecular biology to cell biology



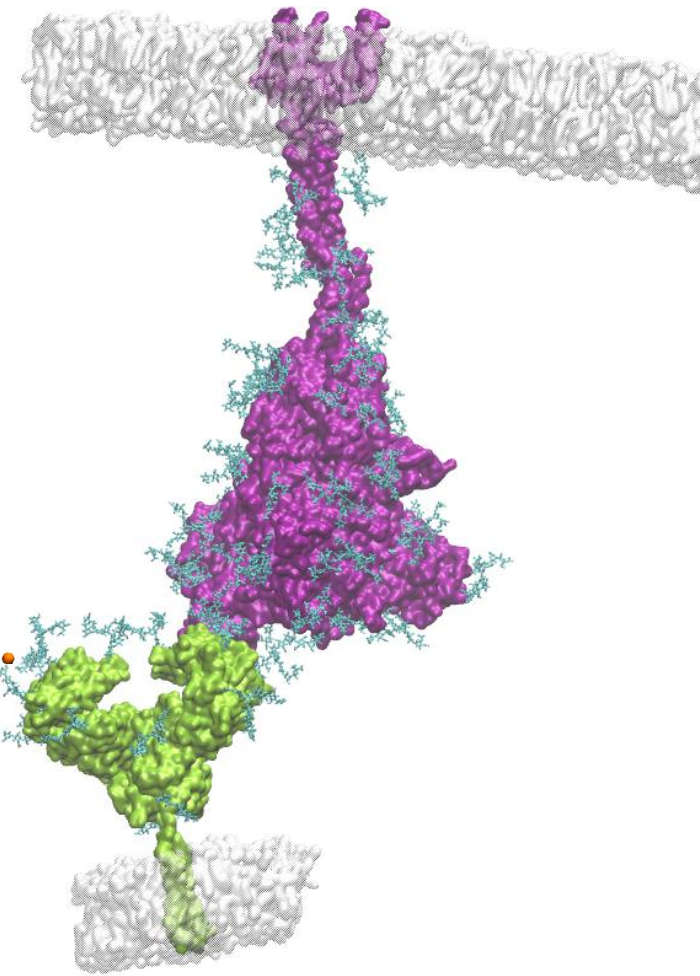
10×10×14 nm
~ 100,000 Atoms



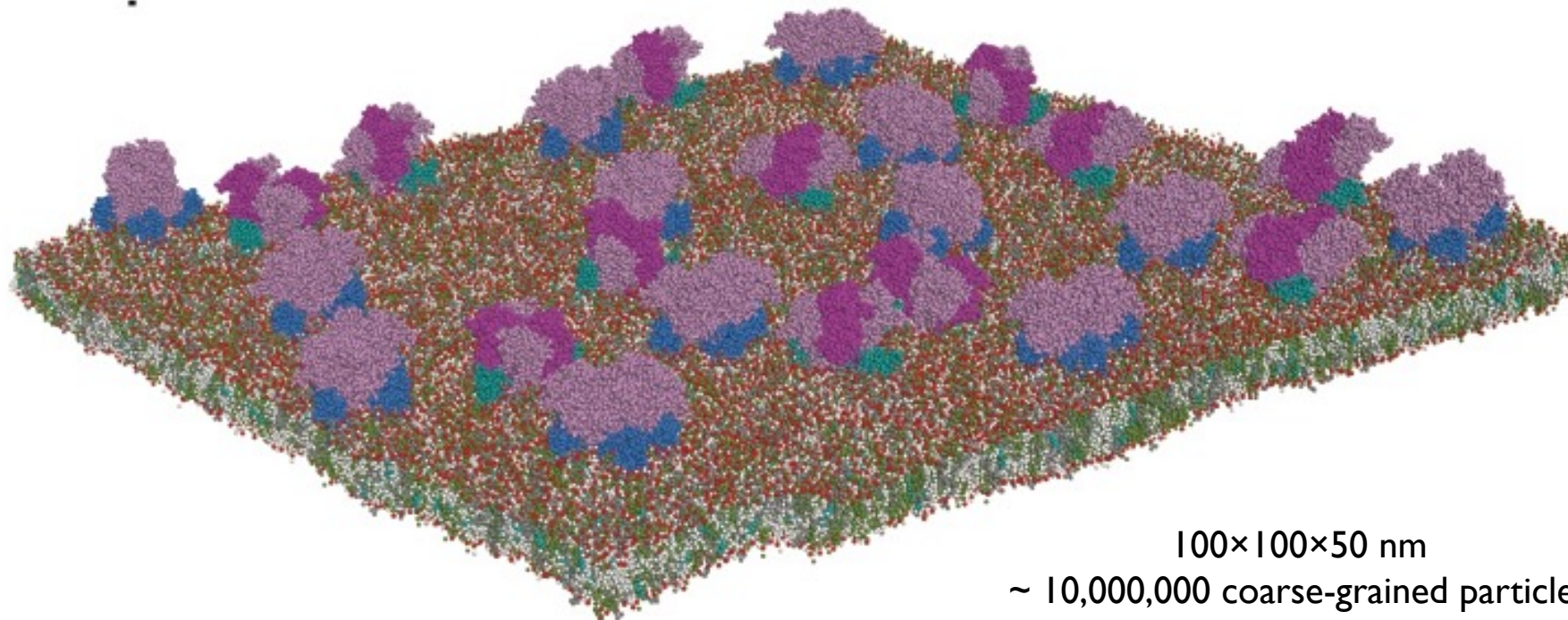
14×14×16 nm
~ 280,000 Atoms



21×21×26 nm
~ 1,000,000 Atoms

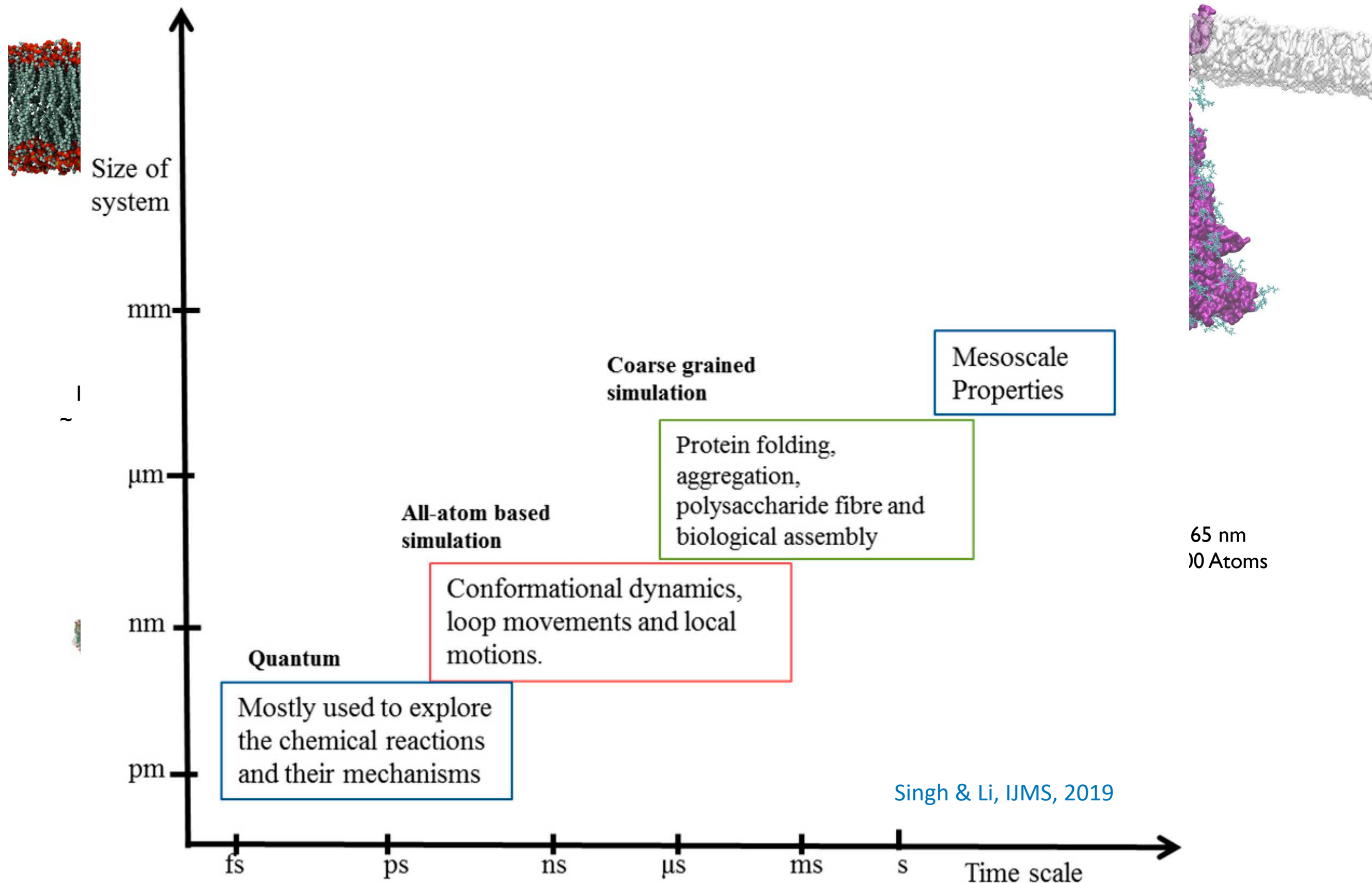


30×30×65 nm
~ 5,000,000 Atoms



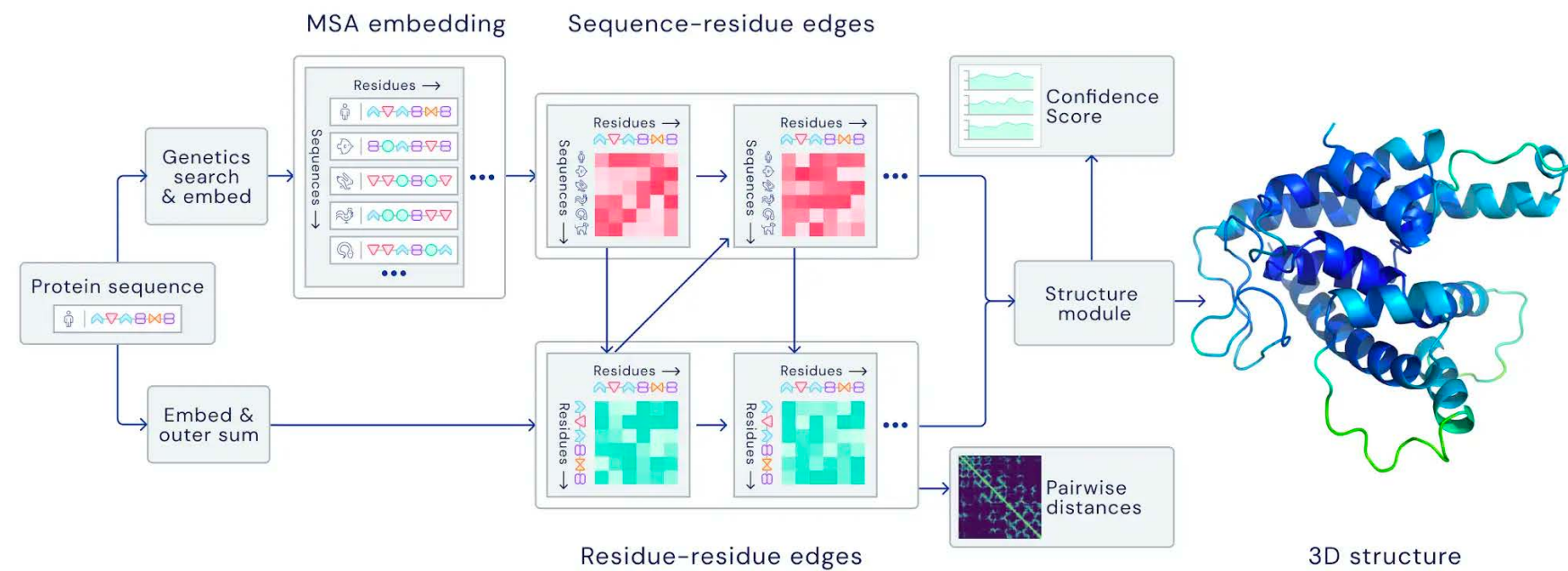
100×100×50 nm
~ 10,000,000 coarse-grained particles

Future: from molecular biology to cell biology

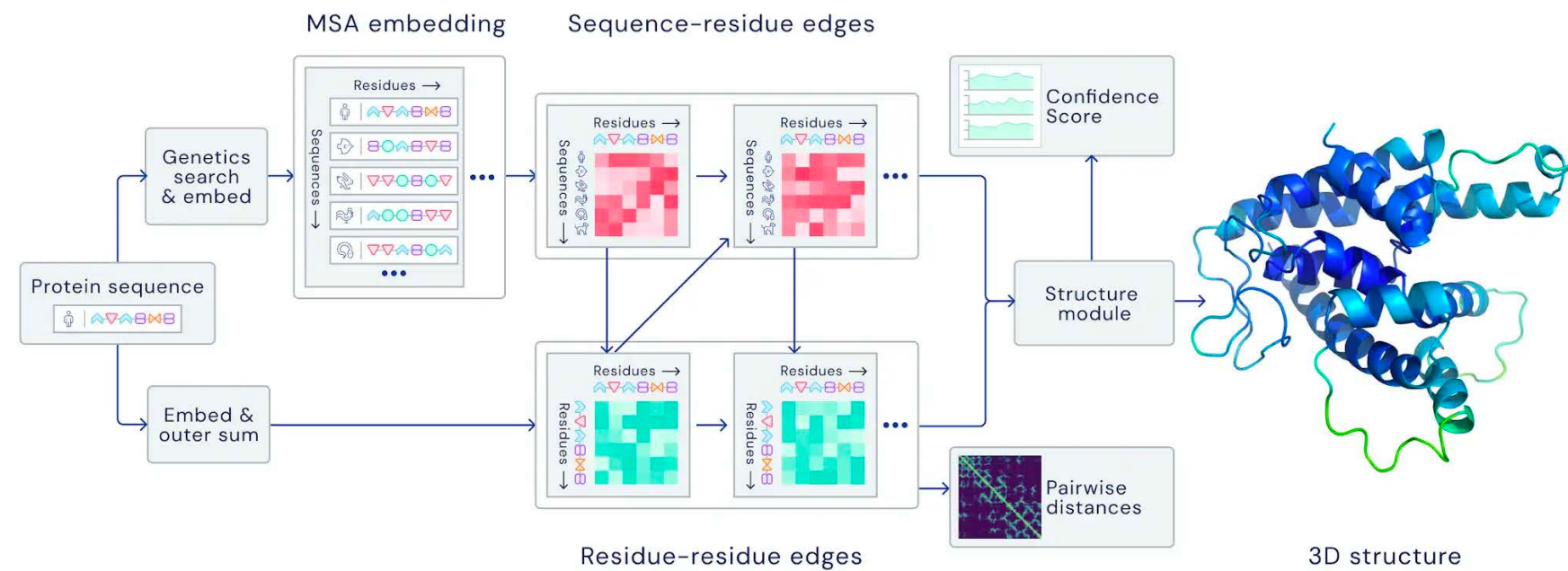


Future: Alphafold and beyond

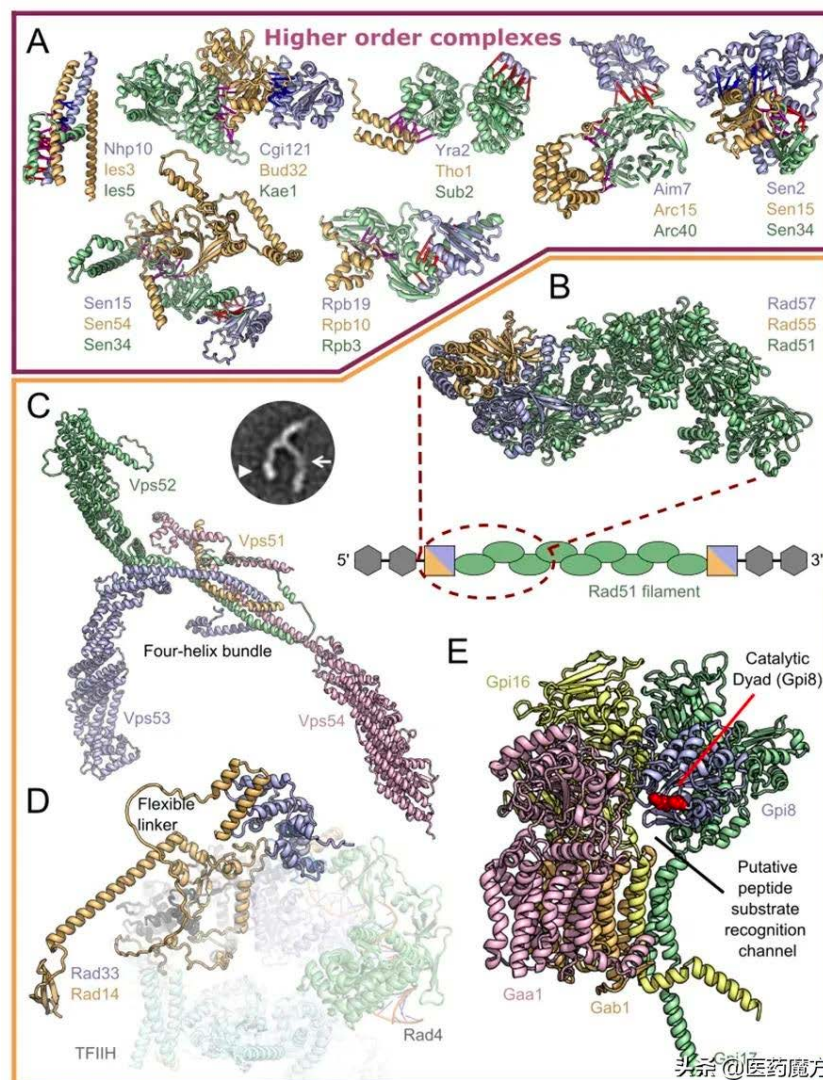
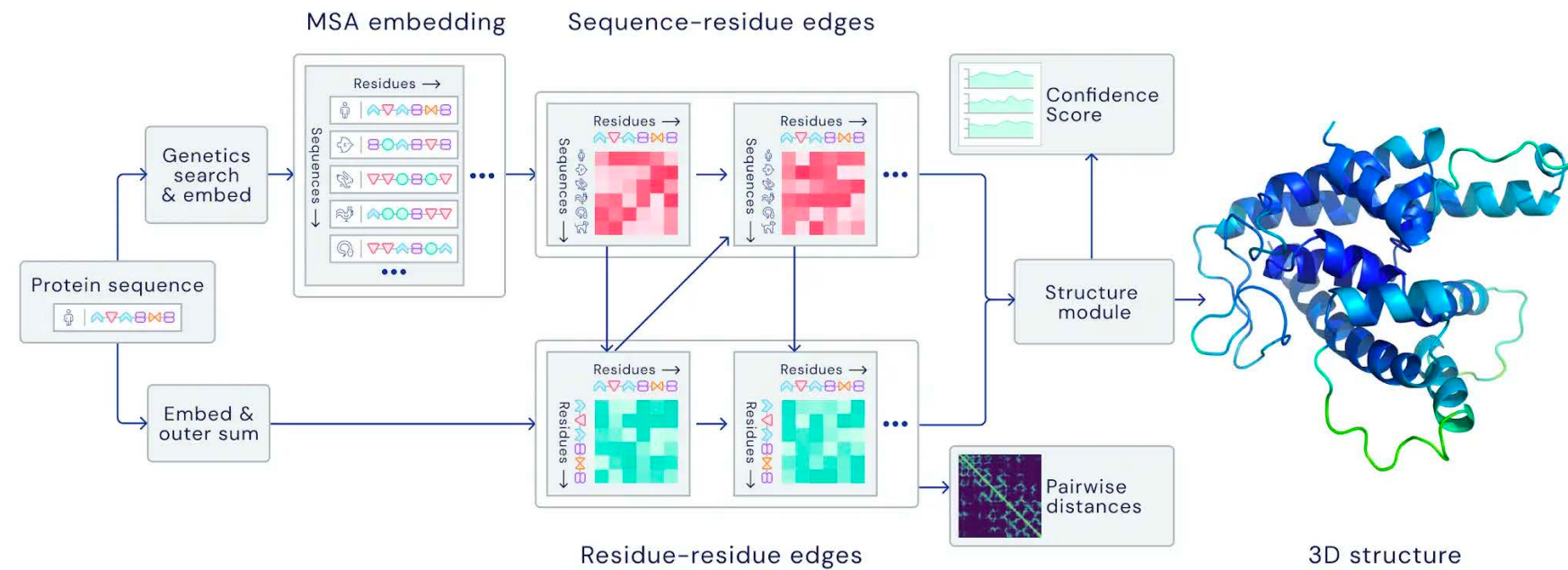
Future: Alphafold and beyond



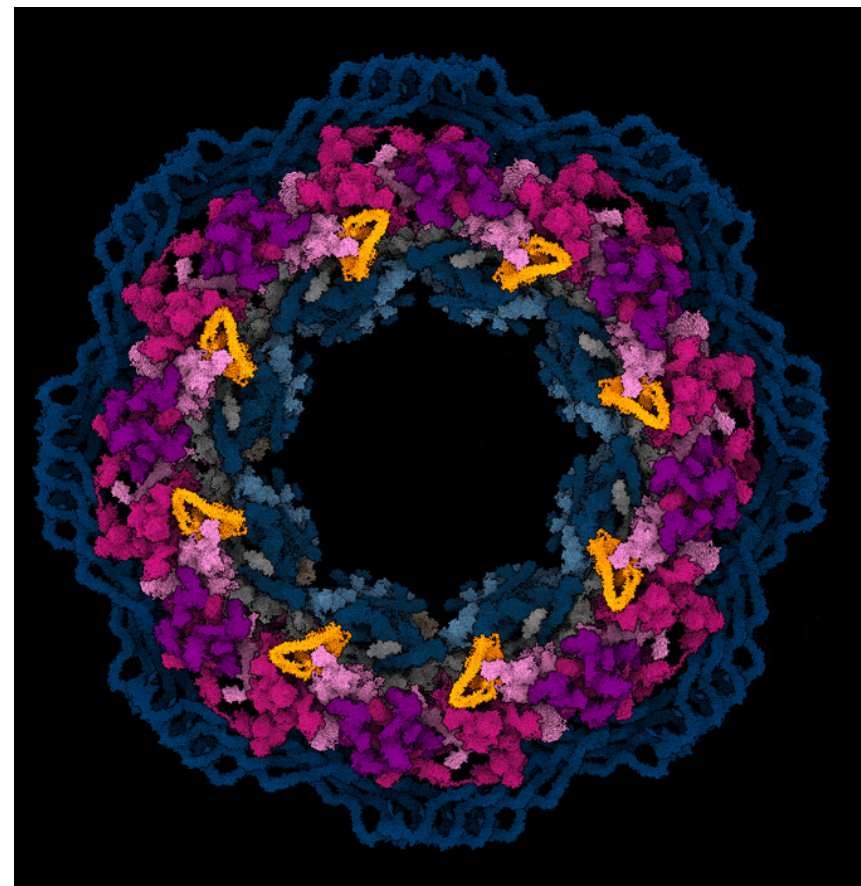
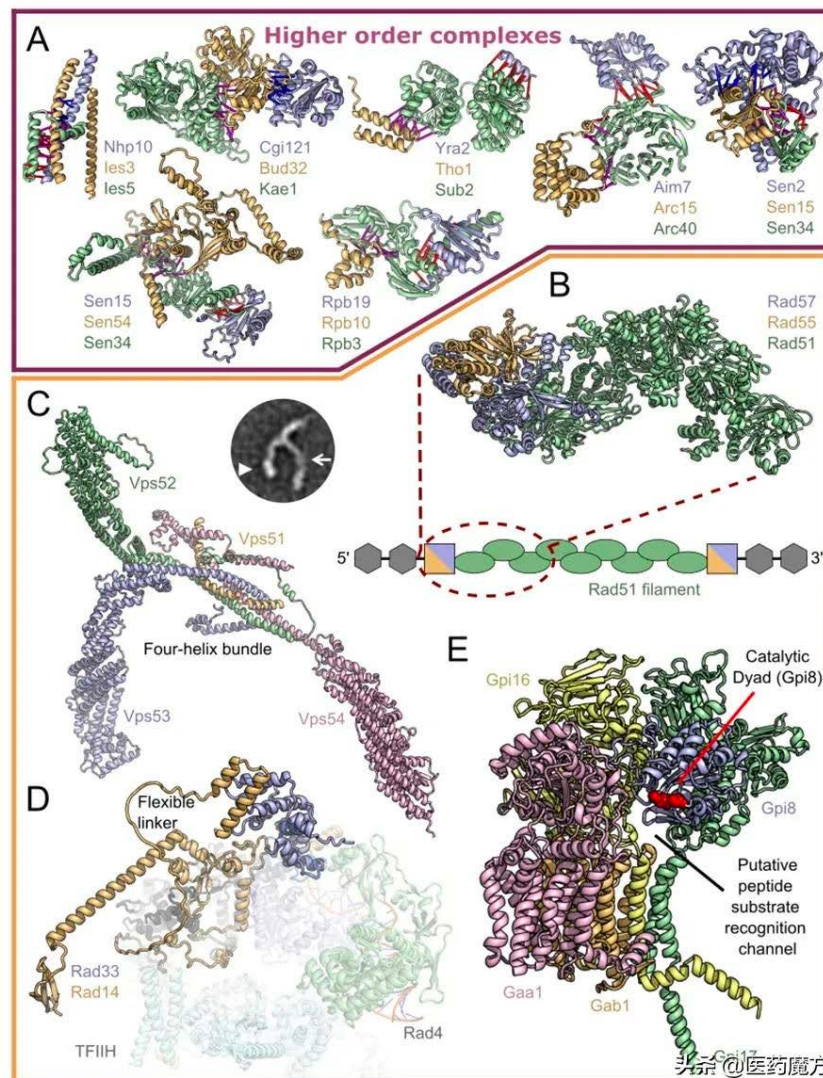
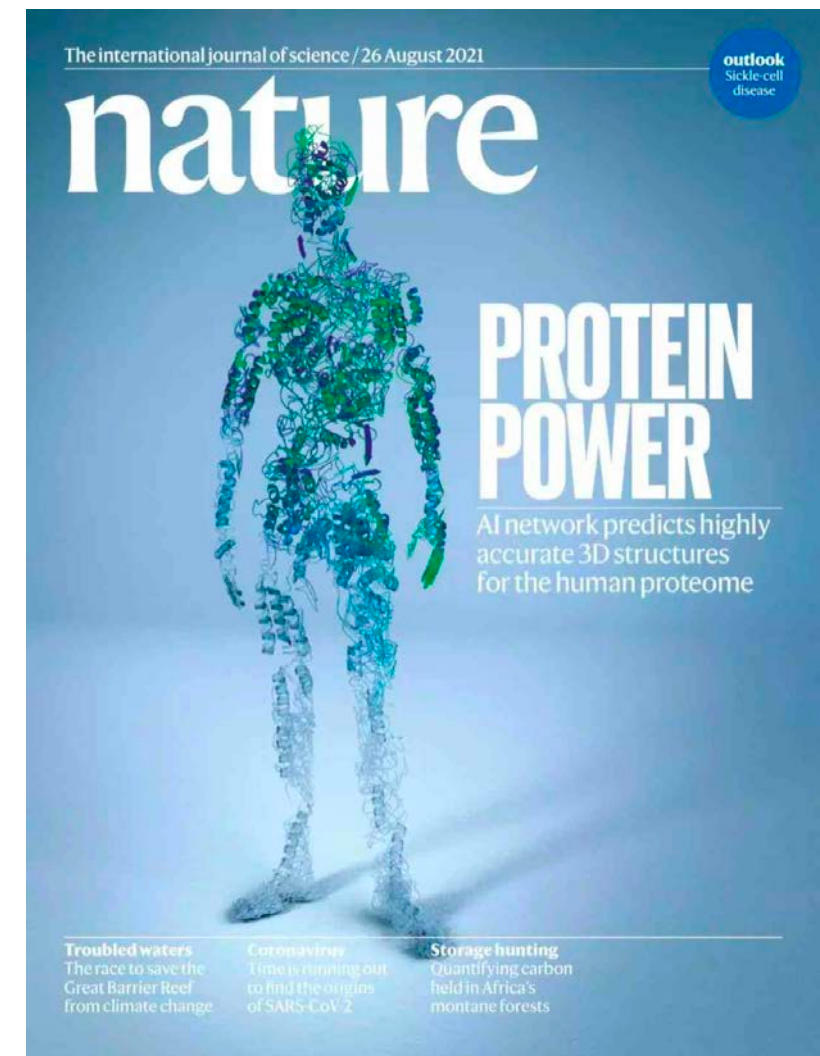
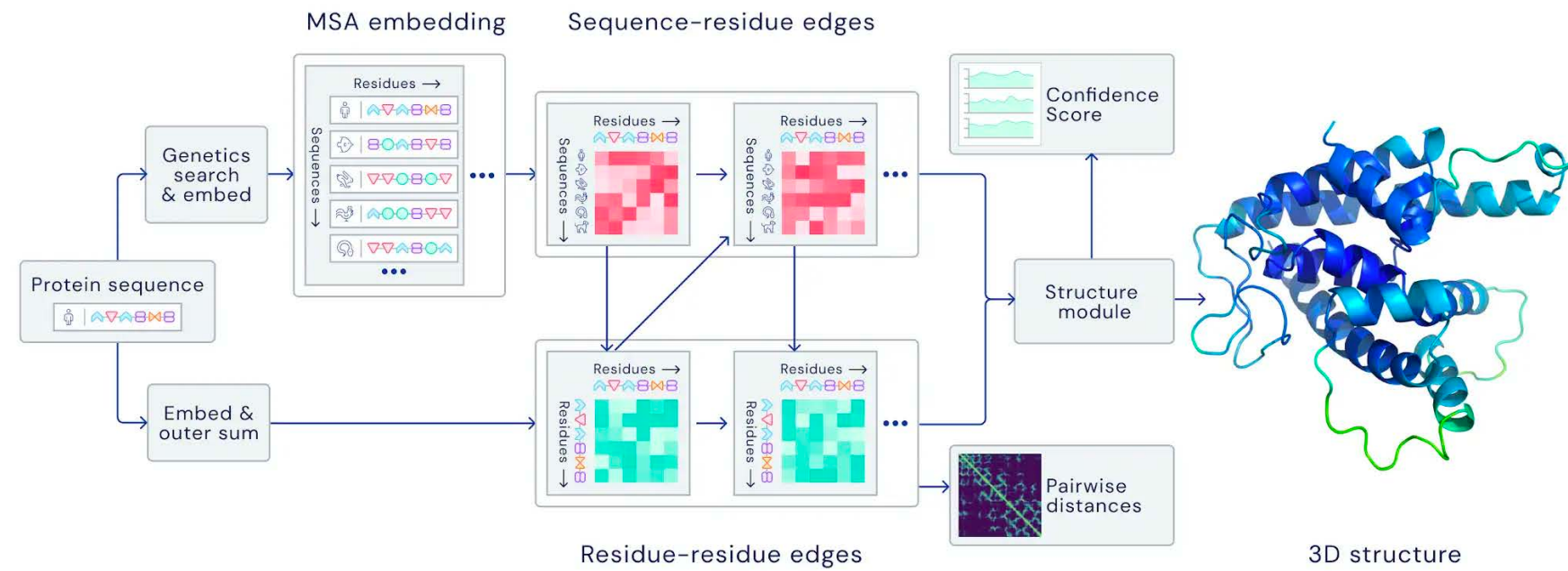
Future: Alphafold and beyond



Future: Alphafold and beyond



Future: Alphafold and beyond



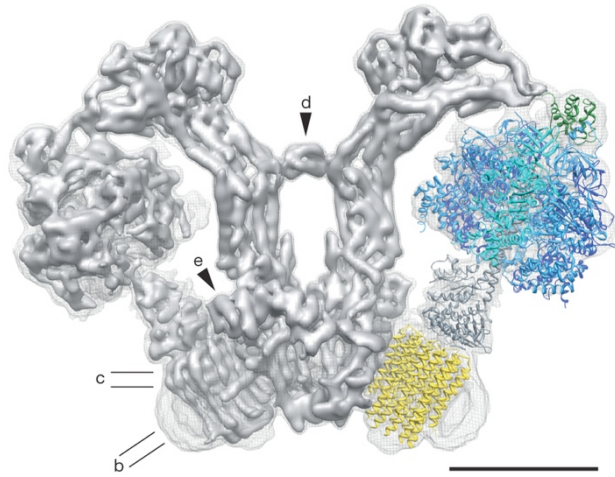
Mosalaganti et al, bioRxiv, 2021

Ahmad Reza Mehdipour

Future: More possibilities

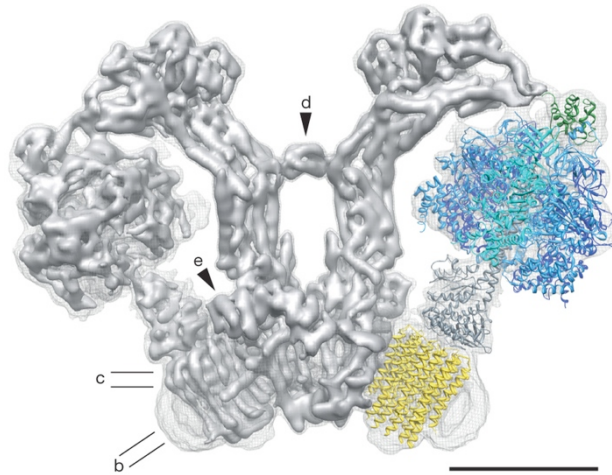
Future: More possibilities

Cryo-electron-microscopy

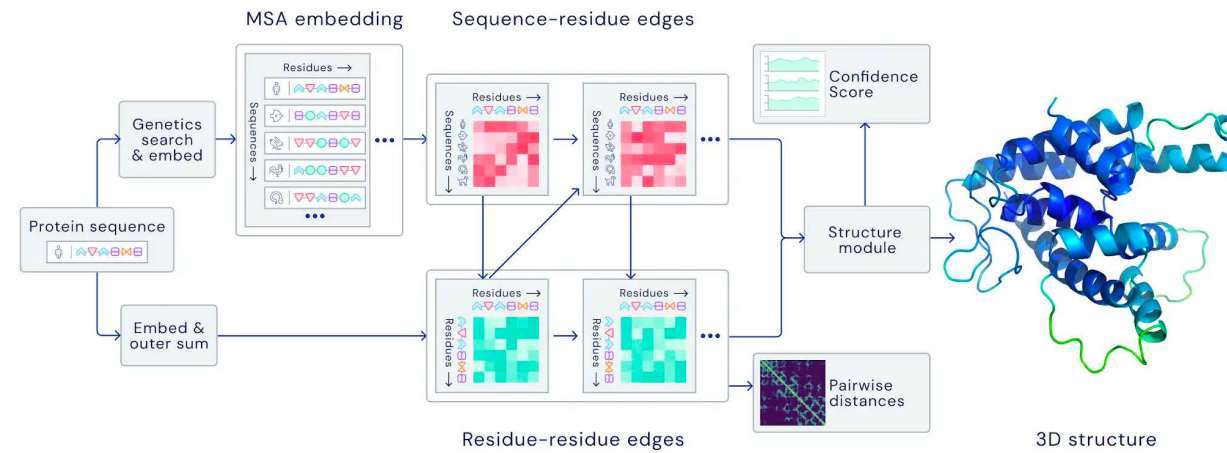


Future: More possibilities

Cryo-electron-microscopy

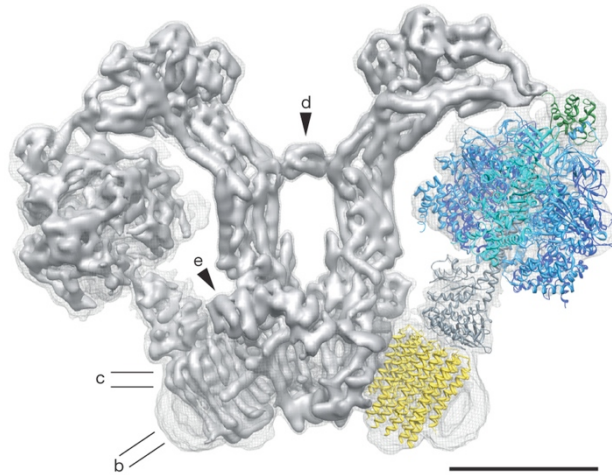


AlphaFold

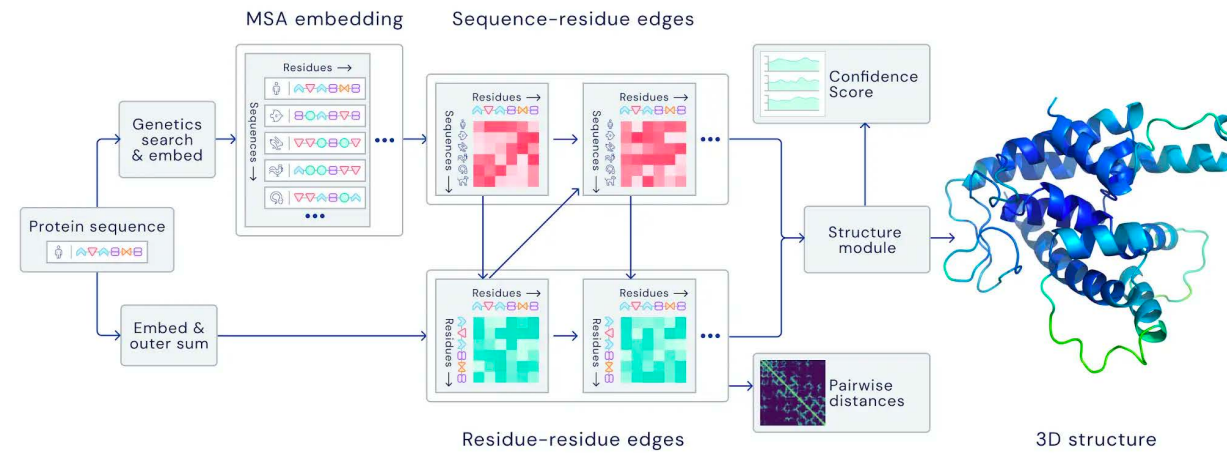


Future: More possibilities

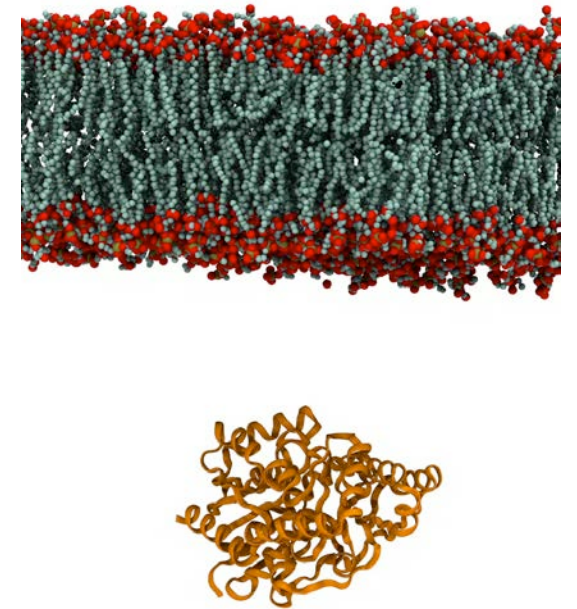
Cryo-electron-microscopy



AlphaFold

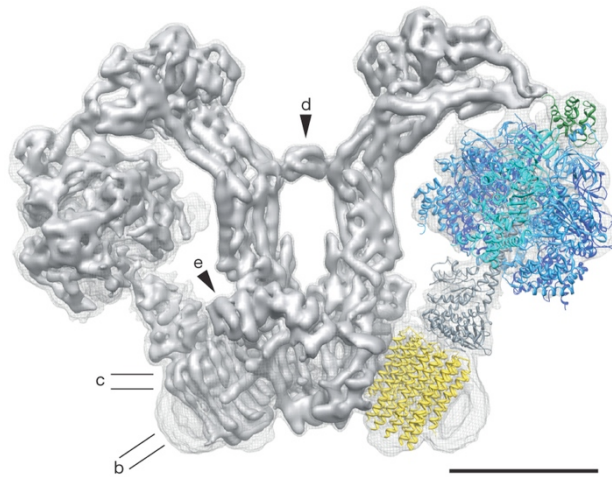


MD simulations

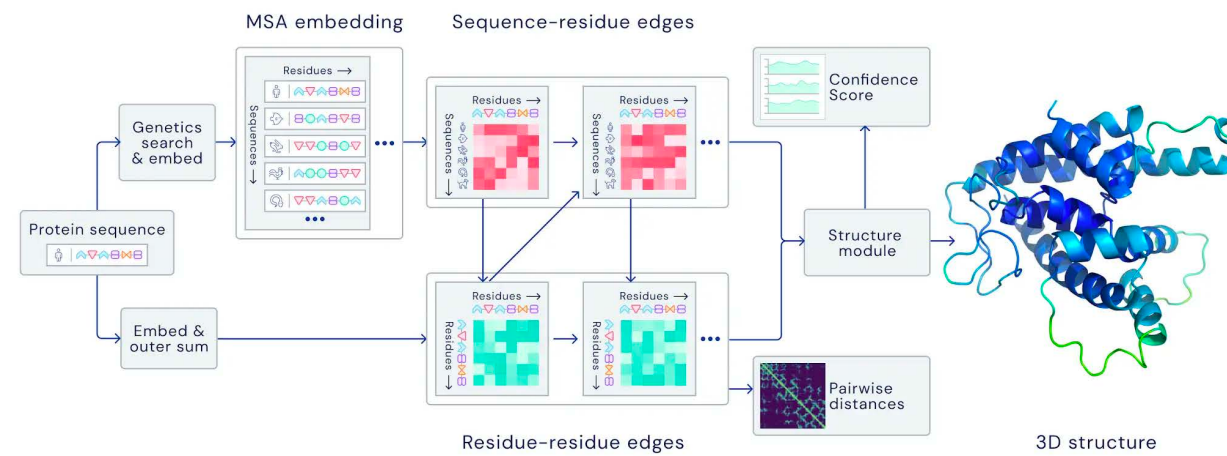


Future: More possibilities

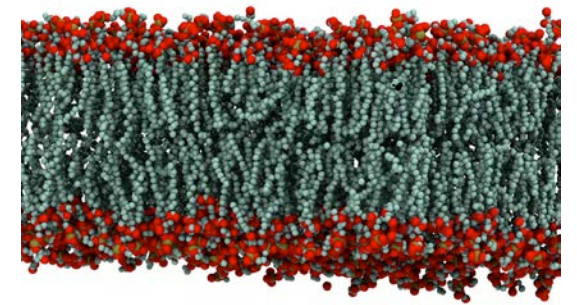
Cryo-electron-microscopy



AlphaFold

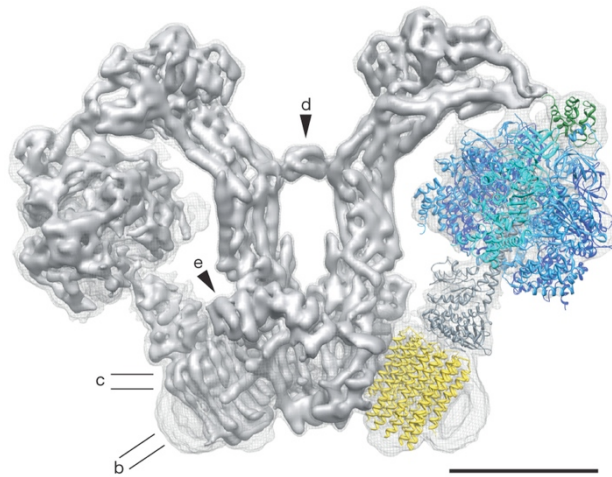


MD simulations

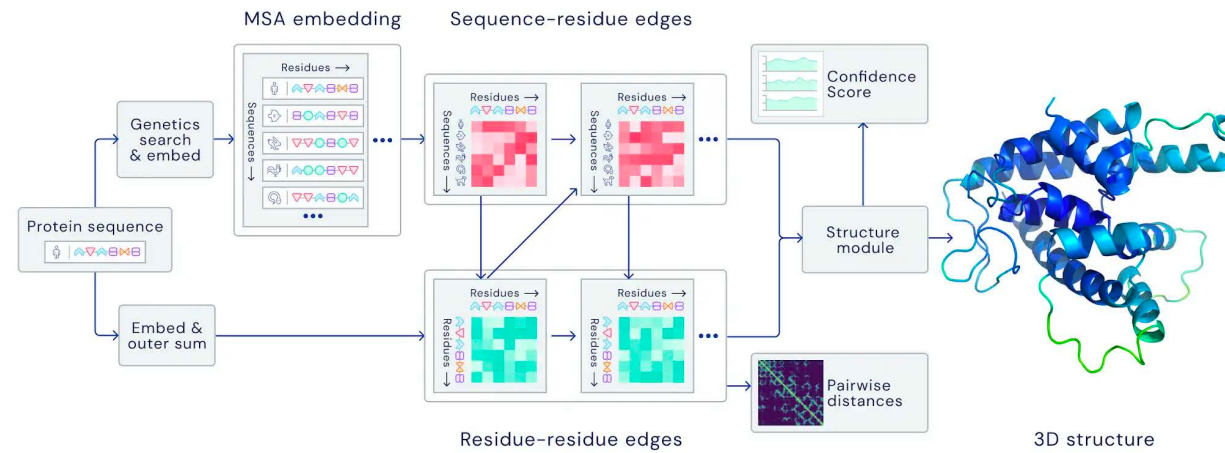


Future: More possibilities

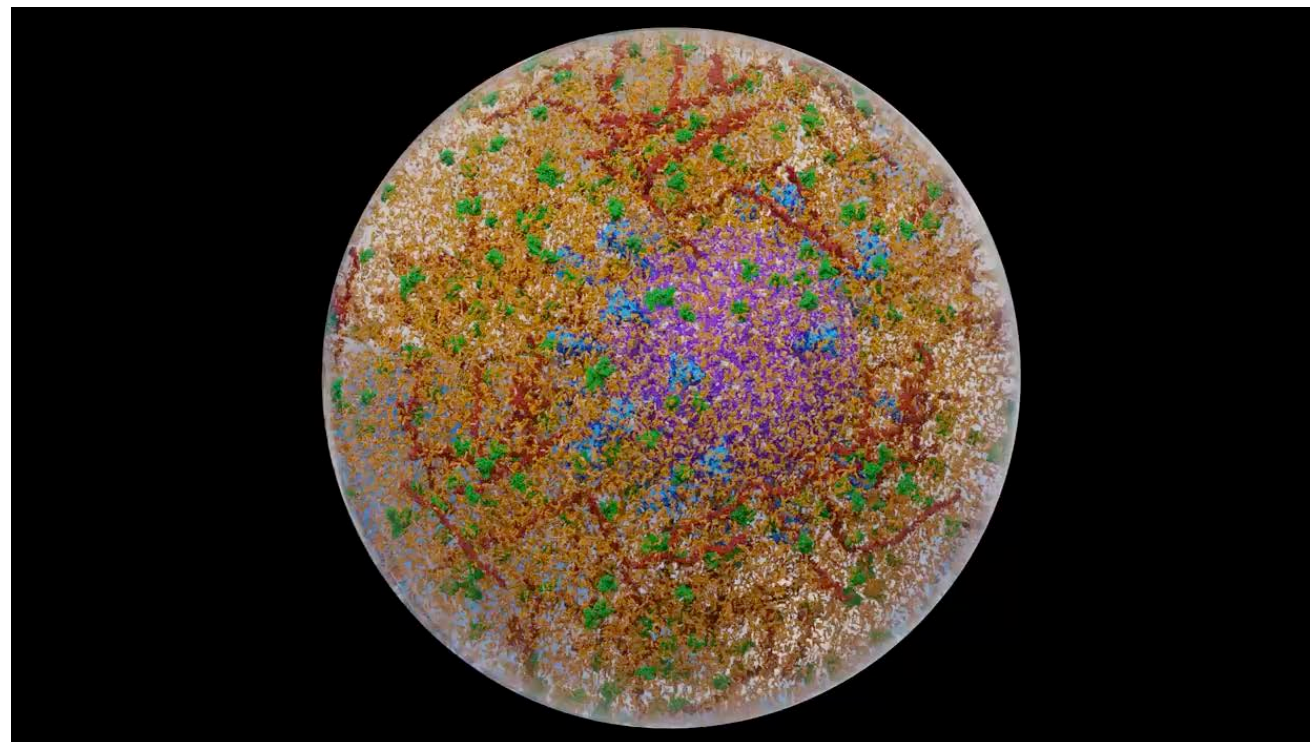
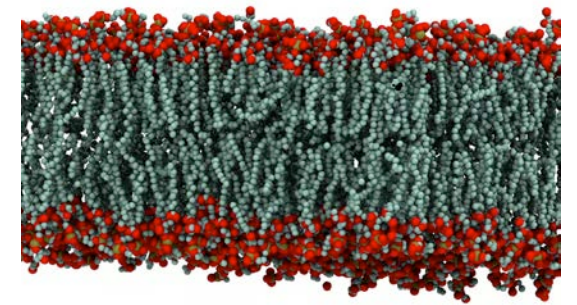
Cryo-electron-microscopy



Alphafold

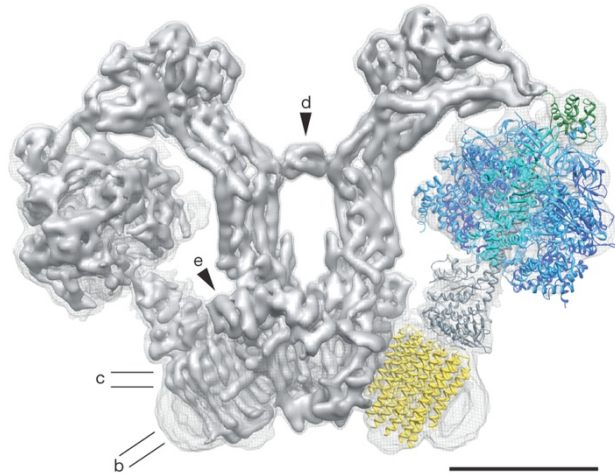


MD simulations

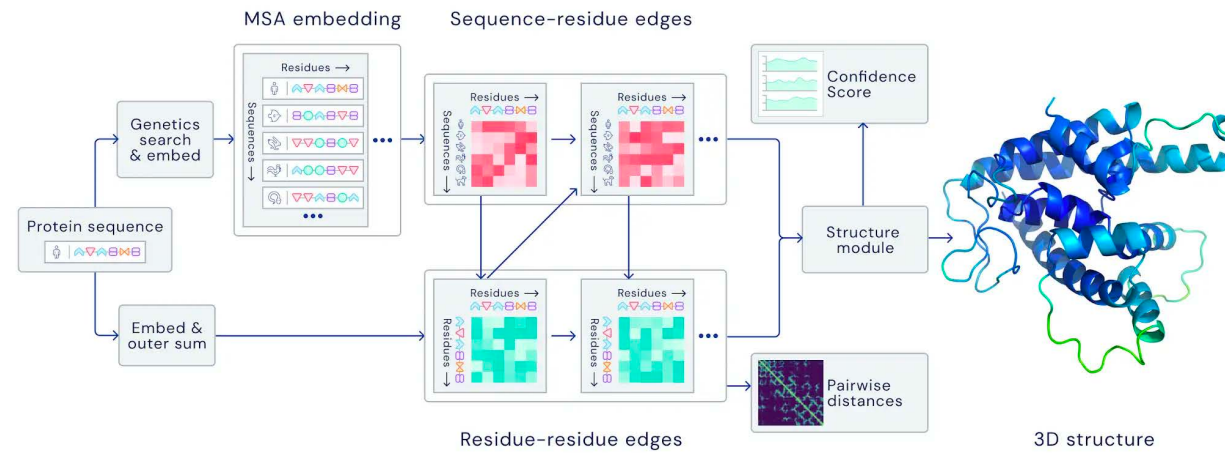


Future: More possibilities

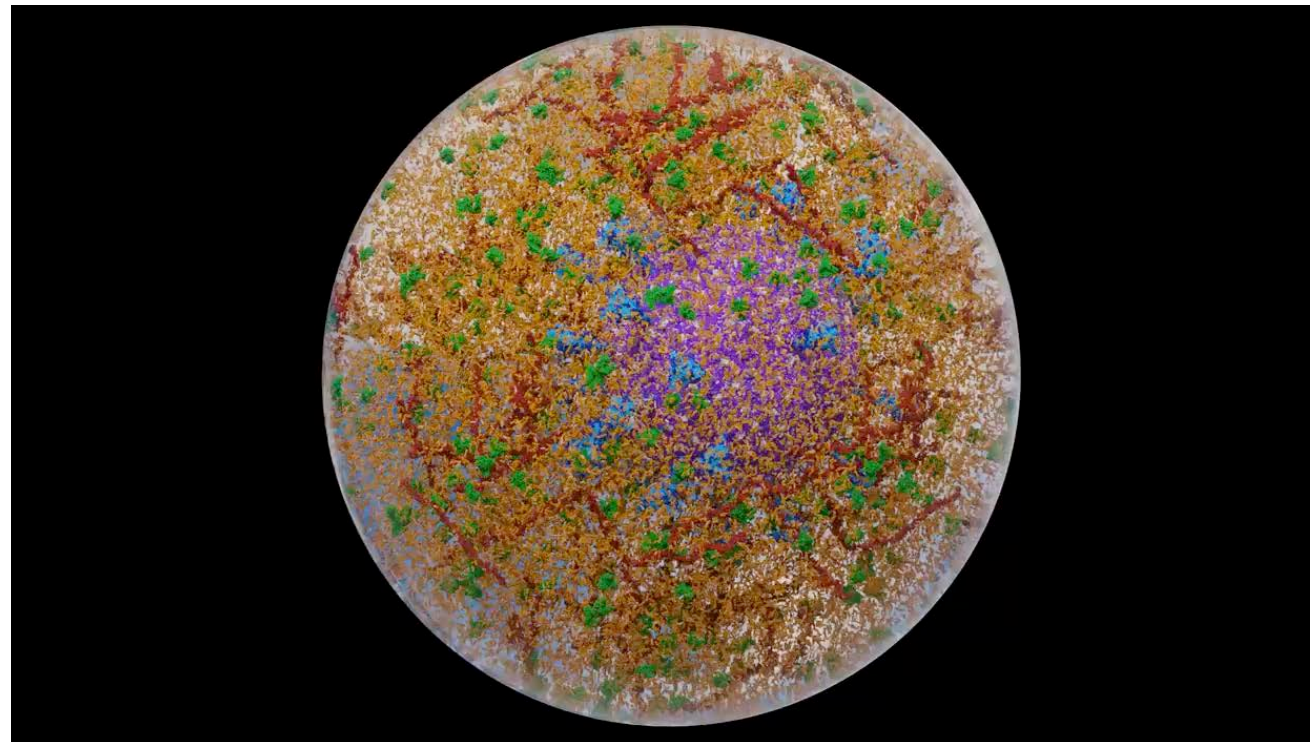
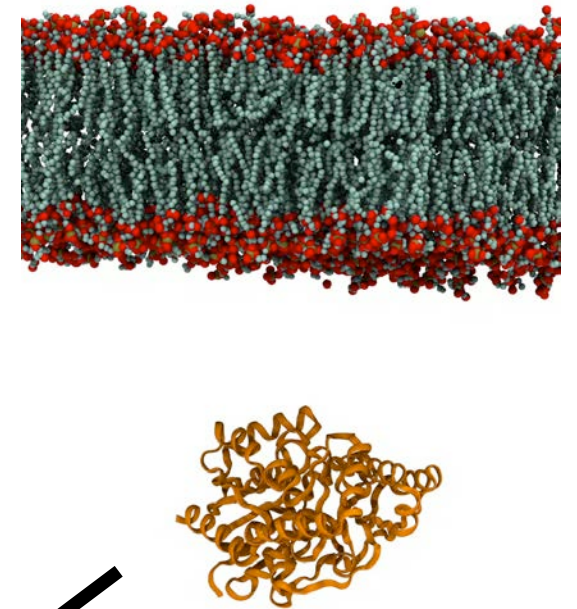
Cryo-electron-microscopy



AlphaFold



MD simulations



Simulation of an aerosol drop containing SARS-CoV2 virus

Total number of atoms: 1.3 billion atoms

Simulation time: 1 μ s

Rommie Amaro Lab, New York Times, 2021

Thank you!